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(71) Applicant *(for all designated States except US)*: **MEDICAL RESEARCH COUNCIL** [GB/GB]; 20 Park Crescent, London W1B 1AL (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KELLY, Rodney, William** [GB/GB]; Medical Research Council Reproductive Biology Unit, University of Edinburgh, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9ET (GB).

(74) Agent: **MILES, John, S.**; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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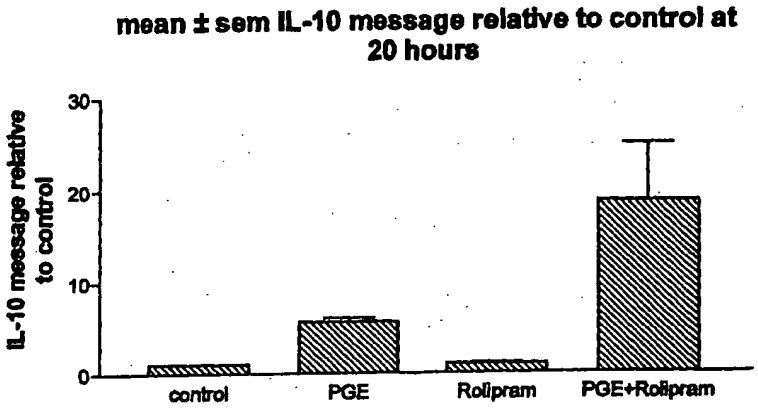

(57) Abstract: A method of inducing tolerance to an antigen in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective phosphodiesterase (PDE) inhibitor.

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THERAPEUTIC METHODS

The present invention relates to therapeutic methods and uses; in particular it relates to methods for inducing tolerance to an antigen in a patient.

An organism's immunity to an antigen arises as a consequence of a first encounter with the antigen and the subsequent production of immunoglobulin molecules, for example, antibodies, capable of selectively binding that antigen. In addition, the immune response is controlled by T cells which may be antigen specific. Immunity allows the rapid recruitment, usually by stimulating an inflammatory response, of cells which can dispose of the foreign antigen. Under certain circumstances, the immune system does not produce an immune response against antigens due to a mechanism called "tolerance". For example, an immune system can normally discriminate against foreign antigens and constituents of the organism itself, due to a mechanism whereby all B lymphocytes which could potentially produce antibodies to constituents of the organism itself ("self antigens") are destroyed during development, thereby removing the organism's capacity to produce antibodies directed to a self antigen.

Tolerance is probably an active process. This means that peripheral tolerance is gained where an antigen is presented to a T cell in a particular environment (*eg* high IL-10 levels and low IL-12 levels). The T cells then circulate and when they meet that specific antigen again they do not mount an immune response (anergic T cells) or they mount a quelling response (regulatory T cells). A role for regulatory T cells has been proposed in tolerance. The regulatory T cells are programmed by the environment of the antigen presenting cell to react to their cognate antigen by releasing "down-regulatory" cytokines. The first such regulatory cells described were induced by IL-10 (Groux *et al.*, 1997, Nature 389:737-742).

Where tolerance breaks down, the organism may produce a cellular immune response (including cytotoxic T cells) to normal constituents of the organism, producing an "autoimmune disease". Examples of autoimmune diseases include systemic lupus erythematosus (SLE), multiple sclerosis (MS) and Hashimoto's disease.

In some circumstances, even the normal response of the immune system to a foreign antigen can produce undesirable results, such as in the case of tissue or organ grafts or transplants, where the immune system of the tissue or organ recipient recognises the tissue or organ graft or transplant as foreign and acts to reject it.

One of the drawbacks of existing methods of treating immune or inflammatory conditions or diseases however, is the limited range of options and their therapeutic inadequacy. For example, glucocorticosteroids used for treating inflammatory respiratory disease have toxic effects in many patients, and alternatives such as cyclosporin A or interferon γ are high-risk, expensive and generally unsatisfactory.

Unexpectedly, the inventor has found that there is a synergistic effect between a prostaglandin and a type IV selective phosphodiesterase (PDE) inhibitor on the release of interleukin-10 (IL-10) from cells of the immune system. Furthermore, the inventor has found that there is a marked stimulation of IL-10 and inhibition of interleukin-12 (IL-12) in cells of the immune system when a prostaglandin and a type IV selective PDE inhibitor are used in combination. In the presence of a type IV selective PDE inhibitor, the stimulation of IL-10 by both PGE and 19-hydroxy PGE was increased strikingly.

Type IV selective PDE inhibitors such as Rolipram are known to raise cAMP and IL-10 levels in monocyte/macrophages stimulated with the bacterial coat product lipopolysaccharide (LPS) (Strassman *et al.*, 1994 *J. Exp. Med.* 180: 2365-70; Kraan *et al.*, 1995 *J. Exp. Med.* 181: 775-9; Kambayashi *et al.*, 1995 *J. Immunol.* 155: 4909-16). Unexpectedly, the inventor has found that there is a synergistic effect between prostaglandin and a type IV selective PDE inhibitor on the release of IL-10 from cells of the immune system, which results in a dramatic increase in the release of IL-10.

The inventor also shows an increase in PDE activity that follows both PGE and 19-hydroxy PGE application. This is a direct negative feedback to reduce the effect of the stimulus. Use of a PGE and a type IV selective PDE inhibitor increases PDE message even further, but then the synthesised phosphodiesterase is nullified by the presence of the inhibitor.

In diseases resulting from an aberrant or undesired immune response there is often a deficiency in IL-10 and/or an increase in IL-12. This imbalance in IL-10 may be detrimental to the development of useful T helper cells, particularly T regulatory cells; a preponderance of type 1 T helper cells over type 2 T helper cells is thought to be characteristic of autoimmune disease. Thus, stimulation of IL-10 production and inhibition of IL-12 is believed to induce a tolerising environment for T cell activation.

The inventor now proposes the use of a type IV selective PDE inhibitor in combination with a prostaglandin or agonist thereof in the induction of tolerance of, or tolerance to, an antigen in a patient.

Furthermore, the combination of a type IV selective PDE inhibitor and a prostaglandin or agonist thereof is considered by the inventor to achieve the

desirable effect of reducing the amount of prostaglandin or agonist thereof or PDE inhibitor required to achieve a useful degree of therapeutic benefit, and/or reducing the side effects of administration of prostaglandin or agonist thereof.

As far as the inventor is aware, there has never been any suggestion that a combination of a prostaglandin or agonist thereof and a type IV selective inhibitor of PDE could be used to stimulate IL-10 production, and there has been no suggestion of a treatment using this combination to stimulate IL-10. Furthermore, there has never been any suggestion that this combination could be used to inhibit IL-12 production, or to induce a tolerising environment for T cell activation, or to induce tolerance to an antigen in a patient.

The use of a combination of a prostaglandin and a PDE inhibitor to alleviate the symptoms of psoriasis and related proliferative skin disorders has been suggested in US 4,034,087, without actually providing any examples of a prostaglandin and a PDE inhibitor being used to treat them. Such an application of a PGE and PDE inhibitor is anti-inflammatory rather than immunomodulatory.

The principal receptor for prostaglandin E2 (PGE2) are the EP_2 and EP_4 sub-types, however other receptor sub-types exist, namely EP_1 and EP_3. EP_2 and EP_4 receptors couple with adenylcyclase and use elevated cAMP as the messenger system. The levels of cAMP in tissue are governed both by synthesis and by catabolism by PDE. PDE can be blocked by specific inhibitors. The inventor believes, but without being bound by any theory, that the administration of a type IV selective PDE inhibitor will enhance the effect of a prostaglandin or agonist thereof in inducing tolerance to an antigen in a patient. Thus, the inventor believes, but without being bound

by any theory that the effect of a prostaglandin or agonist thereof (such as PGE) acting on its EP_2 and EP_4 receptors is to stimulate cAMP and the addition of the type IV selective PDE inhibitor provides a synergistic action on monocytes and macrophages resulting in a reduction in the immune response which is greater than the effect of the sum of the same amount of either prostaglandin or agonist thereof or type IV selective PDE inhibitor administered alone.

A first aspect of the invention provides a method of inducing tolerance to an antigen in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective PDE inhibitor.

By inducing tolerance to an antigen we include the meaning that the immune system of the patient may become tolerant of an antigen where it was intolerant before, or the immune system may mount a reduced response or no response at all (*ie*, an undetectable response) to an immune stimulus such as an antigen.

An effect of the treatment of a patient with a prostaglandin or agonist thereof and a type IV selective PDE inhibitor may be the facilitation or improvement of tolerance to an antigen. The antigen may be one which is foreign to the patient, such as an antigen which is involved in irritable bowel syndrome.

It will also be appreciated that the induction of tolerance to an antigen in a patient upon administration of prostaglandin or agonist thereof and a type IV selective PDE inhibitor may lead to antigen specific immune suppression. Thus, the invention includes a method of inducing tolerance to an antigen in a patient to create a state of immune suppression in the patient, the method comprising administering to the patient a prostaglandin or

agonist thereof and a type IV selective PDE inhibitor. Such a state of immune suppression is characterised by raising the threshold of a cell-mediated immune response to any antigenic stimulus.

Thus, it will be seen that the invention also provides the use of the combination of a prostaglandin or agonist thereof and a PDE inhibitor as an immunosuppressant.

The invention therefore includes suppressing the immune system in a patient. By "suppressing" we include the meaning that the immune system response is altered such the immune system mounts a reduced response or no response to an immune stimulus. Accordingly, the invention includes inducing tolerance to an antigen in a patient leading to amelioration of an aberrant or undesired immune response in the patient.

The method of the invention also includes inducing tolerance to an antigen in a patient for the treatment of diseases or conditions where there is an undesirable immune response.

The invention includes a method of treating an autoimmune disease in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective PDE inhibitor. Such autoimmune diseases include primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastris, Addison's disease, insulin-dependent diabetes mellitus (IDDM), Goodpasture's syndrome, myasthenia gravis, sympathetic ophthalmia, MS, autoimmune haemolytic anaemia, idiopathic leucopenia, ulcerative colitis, dermatomyositis, scleroderma, mixed connective tissue disease, rheumatoid arthritis, irritable bowel syndrome, SLE, Hashimoto's disease, thyroiditis, Behcet's disease, coeliac disease/dermatitis herpetiformis, and demyelinating disease.

In an alternative embodiment, the invention includes a method of treating an autoimmune disease, with the exception of rheumatoid arthritis, in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective PDE inhibitor.

The treatment is believed to combat the undesirable autoimmune response directly, as well as treating the symptoms by directing T cells away from a pro-inflammatory role.

Without being bound by theory, the inventor believes that the methods of the present invention may affect the programming of T cells so that they become regulatory or suppressive T cells rather than pro-inflammatory T cells. When a T cell meets an antigen, in the presence of a prostaglandin and type IV selective PDE inhibitor, it will release a suppressive cytokine such as IL-10 and not an inflammatory cytokine such as IL-12. Treatment with a prostaglandin and type IV selective PDE inhibitor is thus believed to prevent or minimise an inflammatory response from developing. Thus treatment with a prostaglandin and type IV selective PDE inhibitor can be used prophylactically, or as soon as the first symptoms of, *eg* an autoimmune disease, appear. Furthermore, it will be appreciated that because T cells are present throughout the body they may be programmed or primed at a site remote from their ultimate site of action. Similarly, unlike other forms of treatment of certain autoimmune diseases, the method may be helpful in preventing inflammatory responses before they start. Thus, the method may be useful in treating patients who, for example because of their age or genetic factors, are predisposed to an autoimmune disease before any inflammatory symptoms show.

Thus, the invention also includes inducing tolerance to an antigen in a patient for inhibiting or dampening an immune or inflammatory response in the patient. By "inhibition or dampening" we include increasing the level of IL-10, and/or decreasing the level of IL-12 which leads to an increase in the Th2 response a decrease in the Th1 response

The invention also includes inducing tolerance to an antigen in a patient leading to amelioration of an aberrant or undesired inflammatory response in the patient. The aberrant or undesired inflammator response is not associated with psoriasis, or a related proliferative skin disorder.

By "aberrant or undesired immune or inflammatory response" we include diseases or conditions which cause the presence of visible or measurable inflammation within a tissue in an individual or patient. For example, the tissue that forms part of an allograft or the tissues of a host having received an allograft, or the central nervous system of an individual with MS, or insulitis in a patient with type 1 diabetes, swollen joints in a patient with rheumatoid arthritis.

The invention includes a method of inducing tolerance to an antigen in a patient thereby suppressing an aberrant or undesired immune or inflammatory response in the patient, such as a response related to transplant rejection.

The invention therefore includes the treatment of a disease or condition associated with transplant rejection such as graft versus host disease or host versus graft disease, for example in organ or skin transplants. In these cases, an inhibition or dampening of an immune or inflammatory response may be required. Thus, the invention includes the combating of transplant rejection.

Diseases or conditions where there is an aberrant or undesired immune or inflammatory response may also include allergies, wherein the undesired response is an allergic response. In such a condition or disease, the antigen to which tolerance is induced would be an allergen.

Thus, the invention includes a method of treating an allergic condition or disease in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective PDE inhibitor.

The allergy may be any allergy such as allergy to cat dander, house dust mite, grass or tree pollens, fungi, moulds, foods, stinging insects and so on.

In one preferred embodiment, the allergic condition or disease is allergic asthma, and the PG and the type IV selective PDE inhibitor are preferably administered to the lungs or bronchial tree, preferably *via* an aerosol. This embodiment may be particularly advantageous as some 19-hydroxy prostaglandin analogues have been reported to function as bronchodilators, such as those described in US Patent No. 4,127,612, incorporated herein by reference. The reason why PGs are not widely used in the treatment of asthma is that they make the patient cough. Administration of a type IV selective PDE inhibitor would allow the PG to be administered at a lower concentration, thus providing the therapeutic benefits while minimising the side-effects.

Thus the invention includes the use of a PGE or 19-hydroxy PGE and a type IV selective PDE inhibitor for treatment by inhalation of asthma due to allergy.

Whether or not a particular patient is one who is expected to benefit from treatment may be determined by the physician.

The prostaglandin or agonist thereof and the type IV selective PDE inhibitor may be administered in any order. Preferably, they are co-administered. However, they may be administered so that the type IV selective PDE inhibitor can take effect in the accessory cells prior to administration of the prostaglandin or agonist thereof. The prostaglandin or agonist thereof and the type IV selective PDE inhibitor may be administered substantially simultaneously, for example in the same composition. The order and timing of administration may be determined by the physician using knowledge of the properties of the prostaglandin and type IV selective PDE inhibitor. For example, the prostaglandin (such as misoprostol) may be active over a period of 4 hours following administration. The type IV selective PDE inhibitor may take of the order of 30 minutes to take effect after administration. Thus, suitable timings of administration can readily be devised from this information.

Where the tolerance to an antigen is desired to be localised to a particular organ, for example to the skin or the bronchial tree and lungs, it is preferred if the prostaglandin or agonist thereof is administered locally at the site of the condition. The prostaglandin or agonist thereof may be administered as a gel or cream or vapour or spray or in a "patch" in the case of a condition localised to the skin, or as an inhaled vapour or spray where the site is the lungs or bronchial tree.

As is described in more detail below, the prostaglandin or agonist thereof may be administered systemically, such as orally. For example, the prostaglandin or agonist thereof may be administered to the mucosal

immune system, *eg via* a suppository, and is expected to act at mucosal sites remote from administration.

The type IV selective PDE inhibitor may be administered by any suitable route. The type IV selective PDE inhibitor may reach the desired site of inhibition of type IV PDE, which is typically the leukocytes in relation to the present invention using many different routes of administration. Typically, in one embodiment, the type IV selective PDE inhibitor is administered systemically. Suitable forms of systemic administration include oral, transcutaneous or by suppository. The type IV selective PDE inhibitor may be administered to the mucosal immune system, *eg via* a suppository, and is expected to act at mucosal sites remote from administration. Type IV selective PDE inhibitors are orally available, so it may be convenient to administer the type IV selective PDE inhibitor orally.

It is also convenient to administer the type IV selective PDE inhibitor locally. Thus, the type IV selective PDE inhibitor may be delivered locally, such as on the skin, using, for example, a gel or cream or vapour or spray or in a "patch" as described above in relation to the administration of the prostaglandin or agonist thereof. Similarly, in the case of administration to the bronchial tree or lungs it may be administered as a spray or vapour.

In preferred embodiments of the invention, the prostaglandin or agonist thereof and the type IV selective PDE inhibitor may be combined in the same formulation for delivery simultaneously. Thus, the prostaglandin or agonist thereof and the PDE inhibitor may be combined in a gel or a cream or a vapour or spray or "patch" or suppository and administered together to the patient.

In a preferred embodiment, a suppository containing PGE or 19 hydroxy PGE and a type IV selective PDE inhibitor has an enteric coating which only releases the active agents in the bowel when the pH has risen. This sort of preparation has been successful in the delivery of glucocorticoids to the bowel (data sheet for Entocort CR).

Alternatively, the PG and PDE inhibitor can be administered in a capsule or other suitable form that is swallowed. The capsule or other suitable has an enteric coating which is pH sensitive leading to release at an appropriate point in the gastrointestinal tract where it is desired to do so, typically the distal ileum or colon.

Alternatively, the prostaglandin and/or type IV selective PDE inhibitor may be administered directly to the colon or distal ileum *via* a non-soluble tube or pipe system, such as produced by Egalet.

A suppository containing PGE or 19 hydroxy PGE and a type IV selective PDE inhibitor may be effective for treating inflammatory bowel disease, which can be caused by antigen-specific immune responses (Groux *et al*).

The administration of prostaglandin and type IV selective PDE inhibitor to a mucosal site remote from the site of inflammation, *eg* co-administration as a suppository in the treatment of arthritis, may be particularly advantageous as pathologic changes in the gastrointestinal tract can be associated with clinical complaints in multiple organs, including the musculoskeletal system (Alghafeer & Sigal, *Bulletin on the Rheumatic Diseases*, **51(2)**: http://www.arthritis.org/research/bulletin/vol51no2/51_2_printable.asp, incorporated herein by reference). Some reactive arthritis can be triggered by inflammatory bowel diseases, and lymphocytes from the gut mucosa have been reported to migrate to joint tissue in enteropathic arthritis (Salmi

& Jalkanen (2001) *J Immunol.*,166(7): 4650-7, incorporated herein by reference).

The prostaglandin or agonist thereof may be any suitable prostaglandin or agonist thereof. By "prostaglandin or agonist" we mean any compound which acts as a prostaglandin agonist on a prostaglandin receptor. The prostaglandin agonist need not be a prostanoid. Typically, the agonist is one which binds the EP_2 or EP_4 receptor.. It is preferred that the prostaglandin or agonist thereof is one which is able to stimulate cAMP production in macrophages. It is preferred that the prostaglandin is a PGE or a PGI. Preferably, the prostaglandin is not a PGF or agonist thereof. It is preferred that the prostaglandin or agonist thereof is PGE_2 or a synthetic analogue thereof. Synthetic analogues include those modified at position 15 or 16 by the addition of a methyl group or those where the hydroxyl has been transposed from position 15 to position 16. Preferred examples of analogues of prostaglandin include Butaprost (an EP_2 receptor agonist) and 11-deoxy PGE1 (an EP_4 receptor agonist). For the avoidance of doubt, the term "prostaglandin" includes naturally-occurring prostaglandins as well as synthetic prostaglandin analogues.

Suitable prostaglandins or agonists thereof include dinoprostone (sold as Propess by Ferring in Europe and Forest in the USA; sold as Prostin E2 by Pharmacia), gemeprost (sold by Farillon), misoprostol (which is sold as Cytotec by Searle and Pharmacia), alprostadil (which is sold as Caverject by Pharmacia and Viridal by Schwarz and MUSE by AstraZeneca) and limaprost.

Misoprostol is a PGE analogue which has EP2 and EP3 agonist effects. Its chemical structure is (±) methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13-enoate.

An example of a non-prostanoid compound which acts as a prostaglandin agonist is AH23848, an EP4 receptor agonist.

EP2 agonists which may be useful in the practise of the invention include AH13205.

Suitable prostaglandins thereof also include 19-hydroxy PGE1 and 19-hydroxy PGE2. Prostaglandin agonists are described in EP 1 097 922 and EP 1 114 816, incorporated herein by reference.

Suitable prostaglandins or agonists thereof may also include any of the 19-hydroxy prostaglandin analogues described in US Patent No. 4,127,612, incorporated herein by reference.

It is preferred that the prostaglandin is prostaglandin E_2 (PGE_2). Prostaglandins and agonists thereof, including PGE_2, are commercially available, for example from Pharmacia and Upjohn as Prostin E2.

The type IV selective PDE inhibitor may be any suitable type IV selective PDE inhibitor. Preferably, the type IV selective PDE inhibitor inhibits type IV PDEs which are known to be active in cAMP breakdown. By "selective" we mean that the inhibitor inhibits type IV PDE more potently than another type. Preferably, the type IV selective inhibitor is at least 2 times more potent an inhibitor of type IV PDE than another PDE type. More preferably, the type IV selective inhibitor is at least 5 times, 10 times, 20 times, 30 times, 40 times, 50 times, 100 times, 200 times, 500 times or 1000 times more potent an inhibitor of type IV PDE than another PDE type. Typically, the inhibitor is around 5 to 50 times more potent an inhibitor of the PDE type IV than another PDE type. Typically, the inhibitor is 5 to 50

times more potent an inhibitor of type IV PDE than an inhibitor that is considered to be non-selective such as theophylline. Thus, theophylline is 30 times less effective than rolipram.

Preferably, selective inhibition is determined by a comparison of IC_{50} levels (Dousa (1999) *Kidney International* 55: 29-62).

US Patent No. 6,127,378 discloses phenanthridines substituted in the 6 position that are described as selective PDE inhibitors (mainly of type IV), that may be suitable for use in the methods of the invention. The disclosure of US 6,127,378 relating to type IV selective PDE inhibitors is incorporated herein by reference.

Specific (or selective) type IV PDE inhibitors include rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone) and Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone). The IC_{50} for rolipram is 800nM, and the IC_{50} for Ro-20-1724 is 2 μM.

Another suitable PDE type IV selective inhibitor is denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine).

CP 80 633 (Hanifin *et al* (1996) *J. Invest. Dermatol.* **107**, 51-56), CP 102 995 and CP 76 593 are also all potent type IV inhibitors (available from Central Research Division, Pfizer Inc, Groton, CT).

Other high affinity type IV selective PDE inhibitors include CPD 840, RP 73401, and RS 33793 (Dousa, 1999). The high affinity type IV selective PDE inhibitors have a K_i of approximately 1 nM while the lower affinity inhibitors have a K_i of about 1 μM.

The disclosures in Dousa (1999); Müller *et al* (1996, *Trends Pharmacol. Sci.* 17: 294-298); Palfreyman & Souness (1996, *Prog Med Chem* 33: 1-52); Stafford & Feldman (1996, *Annual Reports in Medicinal Chemistry* (vol 31) pp 71-80; Ed. Bristol, Academic Press, NY, USA); and Teixeira *et al* (1997, *Trends Pharmacol. Sci.* 18: 164-171) relating to type IV PDE selective inhibitors are incorporated herein by reference.

Typically, when a type IV PDE-selective inhibitor is administered orally, around 1 to 30 mg is used. Thus, a typical oral dose of rolipram or denbufylline is 1 mg or 5 mg or 10 mg or 30 mg.

In one embodiment the prostaglandin or agonist thereof is administered orally. In particular the prostaglandin or agonist thereof is a prostaglandin analogue which has been modified to reduce its catabolism and which is orally available (such as misoprostol).

Although the type IV selective PDE inhibitor can be administered by any suitable means and by any suitable route, when the prostaglandin or agonist thereof is administered orally it is preferred that the type IV selective PDE inhibitor is also administered orally. It is also preferred if the prostaglandin or agonist thereof and type IV selective PDE inhibitor are administered simultaneously, for example in the same composition.

Thus, in a preferred embodiment, the method of the invention makes use of the oral administration of a prostaglandin analogue which has been modified to reduce its catabolism and which is orally available (such as misoprostol) and the oral administration of the type IV selective PDE inhibitor, such as rolipram. The advantages of oral administration is that it generally has good compliance compared to other modes of administration.

The inventor believes that the combination of type IV selective PDE inhibitor with the orally available prostaglandin or agonist thereof will mean that a lower dose of oral prostaglandin will be required than in the absence of the type IV selective PDE inhibitor. It is believed by the inventor that this will have the advantage of reducing side effects caused by the oral prostaglandin or agonist thereof, such as muscle cramps.

Typically, 0.1 – 100 μg of 19 hydroxy PGE and 1 –250 μg Rolipram in 5 ml saline would be administered.

Typically, 100 to 800 μg of misoprostol is administered orally daily with 1 to 30 mg of rolipram or denbufylline.

As described above, the prostaglandin or agonist thereof can be used orally in combination with a PDE inhibitor at a lower dose than in the absence of PDE inhibitor.

Typically, the dose of type IV selective PDE inhibitor is as described above and the prostaglandin, such as misoprostol, is administered at a dose of 100 to 400 μg.

The data described in the Figures and Examples shows that typically a higher concentration of 19-hydroxy PGE would be necessary to achieve similar effects to PGE. However, 19 hydroxy PGE has the advantage of being more rapidly catabolised.

Thus, preferably, the combination of a type IV selective PDE inhibitor and prostaglandin or agonist thereof, comprises a selective type IV PDE inhibitor and a 19-hydroxy PGE.

A second aspect of the invention provides the use of a prostaglandin or agonist thereof in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered a type IV selective PDE inhibitor. Thus, the patient may already have been administered the type IV selective PDE inhibitor before administration of the prostaglandin or agonist thereof, or is administered the type IV selective PDE inhibitor at the same time as the prostaglandin or agonist thereof or will be administered the type IV selective PDE inhibitor after administration of the prostaglandin or agonist thereof.

A third aspect of the invention is the use of a type IV selective PDE inhibitor in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered a prostaglandin or agonist thereof. Thus, the patient may already have been administered the prostaglandin or agonist thereof before administration of the type IV selective PDE inhibitor, or is administered the prostaglandin or agonist thereof at the same time as the type IV selective PDE inhibitor or will be administered the prostaglandin or agonist thereof after administration of the type IV selective PDE inhibitor.

A fourth aspect of the invention provides the use of a combination of a prostaglandin or agonist thereof and a type IV selective PDE inhibitor in the manufacture of a medicament for inducing tolerance to an antigen in a patient. Thus, the prostaglandin or agonist thereof and type IV selective PDE inhibitor may be combined in the same medicament before administration to the patient.

Preferably, the use according to the second, third and fourth aspects is in treating an aberrant or undesired immune or inflammatory response in the patient.

The preferences for the prostaglandin or agonist thereof, type IV selective PDE inhibitors, routes of administration, doses and so on for the second, third and fourth aspects of the invention are the same as for the first aspect of the invention.

A fifth aspect of the invention provides a therapeutic system for inducing tolerance to an antigen, the system comprising a prostaglandin or agonist thereof and a type IV selective PDE inhibitor. The therapeutic system may also be termed a "kit of parts".

Preferably, the therapeutic system contains a preferred prostaglandin or agonist thereof as defined in the first aspect of the invention. Still preferably, the therapeutic system contains a preferred type IV selective PDE inhibitor as defined in the first aspect of the invention. The therapeutic system or kit of parts may suitably contain both the prostaglandin or agonist thereof and the type IV selective PDE inhibitor packaged and presented in suitable formulations for use in combination, either for administration simultaneously or for administration which is separated in time. Thus, for example, in one embodiment where the prostaglandin or agonist thereof and type IV selective PDE inhibitor are for simultaneous administration locally to the skin, the therapeutic system may contain a gel or cream or spray or vapour or "patch" which contains a combination of prostaglandin or agonist thereof and PDE inhibitor. Alternatively, in another embodiment where the prostaglandin or agonist thereof and type IV selective PDE inhibitor are for separate administration in a particular treatment regime, the prostaglandin or agonist thereof and PDE inhibitor are packaged or formulated separately. For example, the prostaglandin or agonist thereof may be formulated for administration locally using a cream or gel or spray or vapour or "patch",

and the type IV selective PDE inhibitor is packaged or formulated for systemic administration such as oral administration.

The formulations of the prostaglandin or agonist thereof alone or type IV selective PDE inhibitor alone or the combination thereof may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredients used in the invention with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations in accordance with the present invention suitable for oral administration (eg of the type IV selective PDE inhibitor or of a suitable prostaglandin or agonist thereof) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (eg povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (eg sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of

the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethylcellulose in varying proportions to provide desired release profile.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

For local administration to the skin, it may be convenient to formulate the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor in combination with a dispersion agent or an agent which allows for increased transdermal or transmucosal transfer or penetration, such a dimethyl sulphoxide (DMSO) and the like. Suitable agents are ones which are compatible with the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor (*eg* are solvents thereof).

A composition comprising a prostaglandin or agonist thereof and a type IV selective PDE inhibitor is useful in the practice of the invention.

Typically, the composition is packaged and presented for use in medicine. The composition may be used in human or veterinary medicine; preferably, it is used in human medicine.

Typically, the composition further comprises a pharmaceutically acceptable carrier. Thus, a pharmaceutical composition (or formulation as it may be termed) comprising a prostaglandin or agonist thereof, a type IV selective PDE inhibitor and a pharmaceutically acceptable carrier is useful in the practice of the invention. The carrier(s) must be "acceptable" in the sense of being compatible with the composition of the invention and not deleterious to the recipients thereof. Typically, the carriers will be water or saline which will be sterile and pyrogen free.

The patient on which the method or medicament is used is preferably a human although the patient may be any mammal such as a cat, dog, horse, cow, sheep, horse, pig and so on.

It will be appreciated that the method or medicament may be used before symptoms indicating a need to induce tolerance of an antigen becomes apparent in the patient to be treated, or, either alternatively or in addition, the using of the method or medicament may be used after symptoms or signs become apparent. Thus, in the case of a patient receiving an organ or tissue transplant, it may be beneficial to administer the prostaglandin or agonist thereof and type IV selective PDE inhibitor before the transplantation surgery is started. It may be further beneficial to continue the administration during or after completion of the transplant or graft surgery. The necessary dosage may be determined by the physician, according to the degree of tolerance that is required.

It will further be appreciated that each of the prostaglandin or agonist thereof, the type IV selective PDE inhibitor may be administered as a single dose, or in multiple smaller doses which achieve the same therapeutic effect. The frequency of administration may vary according to the convenience of the physician administering the dose or the patient.

Pregnancy is likely to be a contraindication for the present invention. In fact, pregnancy is a contraindication for several prostaglandins including misoprostol. Cytotec (misoprostol) does not cause hypotension, but this may be a possible risk with the method of the invention.

The invention will now be described in more detail with the aid of the following Figures and Examples.

Figure 1

Expression of mRNA for cytokines IL-10 and IL-12 subunit p35. Experiment carried out on U937 cells (pro-monocytes) in the presence of Rolipram at 1 μg/ml = 4 μM and indomethacin 10 μM. The indomethacin prevents prostaglandin synthesis from cells. Note that the effect of PGE+Rolipram is a marked stimulation of IL-10 and an inhibition of IL-12 both for unstimulated and IFNγ stimulated cells. Vertical scale is a measure of mRNA compared to a control sample as measured by real-time quantitative PCR (Taqman).

Figure 2

Figure 2A is a graph showing the effect of PGE and Rolipram on the production of IL-10 mRNA in U937 cells. Figure 2B is a graph showing the effect of LPS, PGE and Rolipram on the production of IL-10 mRNA in U937 cells. Figure 2C is a graph showing the effect of LPS, PGE and Rolipram on IL-10 release from U937 cells. Figure 2D is a graph showing the effect of PGE and Rolipram on IL-10 release from U937 cells.

Figure 3

A graph showing the effect of 19 hydroxy PGE1 and 19 hydroxy PGE2 on the stimulation of IL-10 in the presence and absence of rolipram.

Figure 4

A graph showing the effect of PGE1 and PGE2 on the stimulation of IL-10 in the presence and absence of rolipram.

Figure 5

A graph showing the effect of PGE and 19 hydroxy PGE on the production of phosphodiesterase IV b mRNA in the presence and absence of rolipram.

Example 1: Effect of the combination of PGE and rolipram on IL-10 and IL-12 production by U-937 (promonocyte) cells

U 937 (human monocyte cell line) cells were grown in RPMI (PAA Laboratories) medium with 10% fetal calf serum added (PAA Laboratories). Cells were treated with prostaglandin E 2 at 10^{-6} Molar or with Interferon-γ at 10 ng/ml for 24 hours. Rolipram at 1 μg/ml and indomethacin at 10 μM was present in all wells. Cells were pelleted and the mRNA was extracted with Tri reagent (Sigma, Poole, UK). Total RNA was obtained by addition of chloroform and subsequent isopropanol precipitation. RNA was reverse transcribed with reverse transcriptase (Applied Biosystems) and random hexamers (Applied Biosystems). Probes and primers for IL-10 and IL-12 (p35) were designed using Primer Express (Applied Biosystems) and were as follows:

IL-12 p35 primers
CCACTCCAGACCCAGGAATG
TGTCTGGCCTTCTGGAGCAT
IL-12Probe
TCCCATGCCTTCACCACTCCCAA
IL-10, primers

CTACGGCGCTGTCATCGAT

TGGAGCTTATTAAAGGCATTCTTCA

IL-10 probe

CTTCCCTGTGAAAACAAGAGCAAGGCC

Template was amplified in a Taqman 7700 machine for 40 cycles using FAM/TAMRA dyes on the probe. The Applied Biosystems Kit was used to amplify and detect ribosomal (18S) RNA as a control. After 40 cycles the Ct (related to cycle number at which signal appears) for the FAM and the 18S (VIC) were recorded and absolute relative quantitation was achieved using the formula $2^{-\Delta\Delta Ct}$.

The results of this experiment are described in the legend to Figure 1. They show that there is a synergistic between a prostaglandin (PGE2) and a PDE inhibitor (rolipram) on the release of IL-10 from cells of the immune system and that there is a marked stimulation of IL-10 and inhibition of IL-12 in cells of the immune system when a prostaglandin (PGE2) and a PDE inhibitor (rolipram) are used in combination.

Example 2: Stimulation of IL-10 production is achieved with or without LPS

U 937 cells were grown in RPMI (PAA Laboratories) medium with 10% fetal calf serum added (PAA Laboratories). 2×10^6 cells per flask were treated with prostaglandin E_2 at 10^{-6} Molar or with Rolipram (4×10^{-6}) for 24 hours. Medium was removed at 20 hours and analysed by ELISA. A capture antibody (Pharmingen) was coated onto 96 well plates and culture medium was added each well. A standard curve was created with recombinant IL-10 protein. After incubation and washing, a biotin labelled monoclonal antibody (Pharmingen) was added and following incubation

and washing, peroxidase labelled streptavidin was added. After washing a tetramethyl benzidine substrate was added and colour developed in proportion to IL-10 in the original sample/standard. Colour was read using a plate photometer (Labsystems, Multiskan). Mean concentrations (N=3) in controls with no lipopolysaccharide (LPS) were 38.2pg/ml and in the presence of LPS (100nM) they were 43.9 prostaglandin/ml.

After the incubation (20 hours), cells were pelleted and the mRNA was extracted with Tri-reagent (Sigma, Poole, UK). Total RNA was obtained by addition of chloroform and subsequent isopropanol precipitation. RNA was reverse transcribed with reverse transcriptase (Applied Biosystems) and random hexamers (Applied Biosystems). Probes and primers for IL-10 and IL-12 (p35) were designed using Primer Express (Applied Biosystems) and were as follows:

IL-12 p35 primers
CCACTCCAGACCCAGGAATG
TGTCTGGCCTTCTGGAGCAT
IL-12 probe
TCCCATGCCTTCACCACTCCCAA
IL-10 primers
CTACGGCGCTGTCATCGAT
TGGAGCTTATTAAAGGCATTCTTCA
IL-10 probe
CTTCCCTGTGAAAACAAGAGCAAGGCC

Template was amplified in a Taqman 7700 machine for 40 cycles using FAM/TAMRA dyes on the probe. The Applied Biosystems kit was used to amplify and detect ribosomal (18S) RNA (using VIC/TAMRA dyes) as an internal control in the same reaction tube. After 40 cycles the Ct (related to

cycle number at which signal appears) for the FAM and the 18S (VIC) were recorded and absolute relative quantitation was achieved using the formula $2^{-\Delta\Delta Ct}$ where Δ refers to the difference between the FAM and VIC signal related to an standard comparator included in each run.

Example 3

The effect of PGE1, PGE2, 19 hydroxy PGE1 and 19 hydroxy PGE2 on the stimulation of IL-10 in the presence and absence of rolipram was investigated as described above in Example 2. IL-10 levels were measured using an ELISA assay (R&D Ltd, Oxford). Measurements were taken in accordance with the manufacturer's instructions. Results are shown in Figures 3 and 4.

Example 4

The mRNA for phosphodiesterase IV-b was measured as described in Example 2 above. mRNA was extracted after four hours of incubation. The concentration of the PGE was 1×10^{-6} and that of the 19-hydroxy PGE_2 was 5×10^{-6}. The following primers and Taqman probe were used for quantitation of PDE IV b mRNA.

Forward
CCTTCAGTAGCACCGGAATCA
Reverse
CAAACAAACACACAGGCATGTAGTT
Probe
AGCCTGCAGCCGCTCCAGCC

Results are shown in Figure 5. An increase in PDE activity follows both PGE and 19-hydroxy PGE application, which appears to be a direct

negative feedback to reduce the effect of the stimulus. Use of a PGE and a type IV selective PDE inhibitor increases PDE message levels even further, but then the synthesised phosphodiesterase is nullified by the presence of the inhibitor.

5

Example 5: Treatment of rheumatoid arthritis

A patient with rheumatoid arthritis is administered 800 μg misoprostol and 25 mg rolipram orally, daily.

10

Example 6: Treatment of demyelinating disease

A patient with demyelinating disease is administered 800 μg misoprostol and 25 mg rolipram orally, daily.

CLAIMS

1. A method of inducing tolerance to an antigen in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective phosphodiesterase (PDE) inhibitor.

2. A method according to Claim 1 wherein the prostaglandin or agonist thereof is any one of a prostaglandin E, such as prostaglandin E_2 or an analogue thereof, dinoprostone, gemeprost, misoprostol, alprostadil, limaprost, butaprost, 11-deoxy PGE1, AH23848, AH13205, 19-hydroxy PGE1 or 19-hydroxy PGE2.

3. A method according to Claim 1 or 2 wherein the prostaglandin is a 19-hydroxy PGE.

4. A method according to any one of the preceding claims wherein the type IV selective PDE inhibitor is any one of rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone), denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine), CDP 840, RP 73401 or RS 33793.

5. A method according to any one of the preceding claims wherein the prostaglandin or agonist thereof and the type IV selective PDE inhibitor are administered simultaneously.

6. A method according to any one of the preceding claims wherein the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor is administered locally at a site where tolerance is required.

7. A method according to any one of the preceding claims wherein the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor is administered systemically.

8. A method according to Claim 7 wherein the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor is administered orally.

9. A method according to Claim 7 wherein the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor is administered as a suppository or capsule.

10. A method according to Claim 9 wherein the suppository or capsule has an enteric coating for release of the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor in the bowel of the patient.

11. A method according to Claim 10 for treating inflammatory bowel disease.

12. A method according to any one Claims 1 to 9 for combating a disease or condition associated with transplant rejection.

13. A method according to Claim 12 wherein the disease or condition associated with transplant rejection comprises graft versus host disease or host versus graft disease.

14. A method according to Claim 12 or 13 wherein the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor are administered prior to the transplant.

15. A method according to any one of Claims 1 to 9 for treating an autoimmune disease.

16. A method according to Claim 15 wherein the autoimmune disease is selected from primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastris, Addison's disease, insulin-dependent diabetes mellitus (IDDM), Goodpasture's syndrome, myasthenia gravis, sympathetic ophthalmia, multiple sclerosis (MS), autoimmune haemolytic anaemia, idiopathic leucopenia, ulcerative colitis, dermatomyositis, scleroderma, mixed connective tissue disease, rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythromatosus (SLE), Hashimoto's disease, thyroiditis, Behcet's disease, coeliac disease/dermatitis herpetiformis, and demyelinating disease.

17. A method according to any one of Claims 1 to 9 for treating an allergic disease or condition in the patient.

18. A method according to Claim 17 wherein the allergic disease or condition is allergic asthma.

19. A method according to Claim 18 wherein the prostaglandin is a 19-hydroxy PGE, and wherein the 19-hydroxy PGE, and optionally the type IV selective PDE inhibitor, are administered *via* an aerosol to the bronchial tree or lungs of the patient.

20. A method according to any one of the previous claims wherein the tolerance to the antigen is to treat an aberrant or undesired immune response to the antigen in the patient.

21. A method according to Claim 20 wherein the aberrant or undesired immune response involves a deficiency in IL-10 production and/or an increase in IL-12 production.

22. Use of a prostaglandin or agonist thereof in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered a type IV selective PDE inhibitor.

23. Use of a type IV selective PDE inhibitor in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered a prostaglandin or agonist thereof.

24. Use of a combination of a prostaglandin or agonist thereof and a type IV selective PDE inhibitor in the manufacture of a medicament for inducing tolerance to an antigen in a patient

25. Use according to any one of Claims 22 to 24 wherein the PDE inhibitor selective for type IV PDE is any one of rolipram, CP80 633, CP102 995, CP76 593, Ro-20-1724, denbufylline, CDP 840, RP 73401 or RS 33793.

26. Use according to any one of Claims 22 to 25 wherein the prostaglandin or agonist thereof is any one of a prostaglandin E, such as prostaglandin E_2 or an analogue thereof, carboprost, dinoprostone, gemeprost, misoprostol, alprostadil, lamaprost, butaprost, 11-deoxy PGE1, AH23848, AH13205, 19-hydroxy PGE1 or 19-hydroxy PGE2 or agonist thereof.

27. Use according to any one of Claims 22 to 26 wherein the prostaglandin is a 19-hydroxy PGE.

28. Use according to any one of Claims 22 to 27 wherein the medicament is administered locally at a site where tolerance is required.

29. Use according to any one of Claims 22 to 28 wherein the medicament is formulated to be administered systemically.

30. Use according to Claim 29 wherein the medicament is formulated to be administered orally.

31. Use according to Claim 29 wherein the medicament is formulated as a suppository or capsule.

32. Use according to Claim 31 wherein the suppository or capsule has an enteric coating for release of the prostaglandin or agonist thereof and/or type IV selective PDE inhibitor in the bowel of the patient.

33. Use according to Claim 32 for treating inflammatory bowel disease.

34. Use according to any one of Claims 22 to 31 for combating a disease or condition associated with transplant rejection.

35. Use according to Claim 34 wherein the disease or condition associated with transplant rejection comprises graft versus host disease or host versus graft disease.

36. Use according to Claim 34 or 35 wherein the medicament is administered prior to the transplant.

37. Use according to any one of Claims 22 to 31 for treating an autoimmune disease.

38. Use according to Claim 37 wherein the autoimmune disease is selected from primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastris, Addison's disease, IDDM, Goodpasture's syndrome, myasthenia gravis, sympathetic ophthalmia, MS, autoimmune haemolytic anaemia, idiopathic leucopenia, ulcerative colitis, dermatomyositis, scleroderma, mixed connective tissue disease, rheumatoid arthritis, irritable bowel syndrome, SLE, Hashimoto's disease, thyroiditis, Behcet's disease, coeliac disease/dermatitis herpetiformis, and demyelinating disease.

39. Use according to any one of Claims 22 to 31 for treating an allergic disease or condition in the patient.

40. Use according to Claim 39 wherein the allergic disease or condition is allergic asthma.

41. Use according to Claim 40 wherein the prostaglandin is a 19-hydroxy PGE, and wherein the medicament is formulated as an aerosol for administration to the bronchial tree or lungs of the patient.

42. Use according to any one of Claims 22 to 41 wherein the tolerance to the antigen is to treat an aberrant or undesired immune response to the antigen in the patient.

43. Use according to Claim 42 wherein the aberrant or undesired immune response involves a deficiency in IL-10 production and/or an increase in IL-12 production.

44. A therapeutic system for inducing tolerance to an antigen in a patient, the system comprising a prostaglandin or agonist thereof and a type IV selective PDE inhibitor.

45. A therapeutic system according to Claim 44 wherein the type IV selective PDE inhibitor is in a preparation for systemic administration.

46. A therapeutic system according to Claim 45 wherein the type IV selective PDE inhibitor is in a preparation for oral delivery.

47. A therapeutic system according to any one of Claims 44 to 46 wherein the prostaglandin or agonist is in a preparation for systemic administration, such as oral administration.

48. A therapeutic system according to any one of Claims 44 to 47 wherein the prostaglandin or agonist thereof is any one of a prostaglandin E, such as prostaglandin E_2 or an analogue thereof, dinoprostone, gemeprost, misoprostol, alprostadil, lamaprost, butaprost, 11-deoxy PGE1, AH23848, AH13205, 19-hydroxy PGE1 or 19-hydroxy PGE2.

49. A therapeutic system according to any one of Claims 44 to 48 wherein the prostaglandin is a 19-hydroxy PGE.

50. A therapeutic system according to any one of Claims 44 to 49 wherein the type IV selective PDE is any one of rolipram, CP80 633, CP102 995, CP76 593, Ro-20-1724, denbufylline, CDP 840, RP 73401 or RS 33793.

51. A therapeutic system according to any one of Claims 44 to 50 for combating a disease or condition associated with transplant rejection.

52. A therapeutic system according to Claim 51 wherein the disease or condition associated with transplant rejection comprises graft versus host disease or host versus graft disease.

53. A therapeutic system according to Claim 51 or 52 wherein the prostaglandin or agonist thereof and/or PDE inhibitor are for administration prior to the transplant.

54. A therapeutic system according to any one of Claims 44 to 50 for treating an autoimmune disease.

55. A therapeutic system according to Claim 54 wherein the autoimmune disease is selected from primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastris, Addison's disease, IDDM, Goodpasture's syndrome, myasthenia gravis, sympathetic ophthalmia, MS, autoimmune haemolytic anaemia, idiopathic leucopenia, ulcerative colitis, dermatomyositis, scleroderma, mixed connective tissue disease, rheumatoid arthritis, irritable bowel syndrome, SLE, Hashimoto's disease and thyroiditis, Behcet's disease, coeliac disease/dermatitis herpetiformis, and demyelinating disease.

56. A therapeutic system according to any one of Claims 44 to 50 for treating an allergic disease or condition in the patient.

57. A therapeutic system according to Claim 56 wherein the allergic disease or condition is allergic asthma.

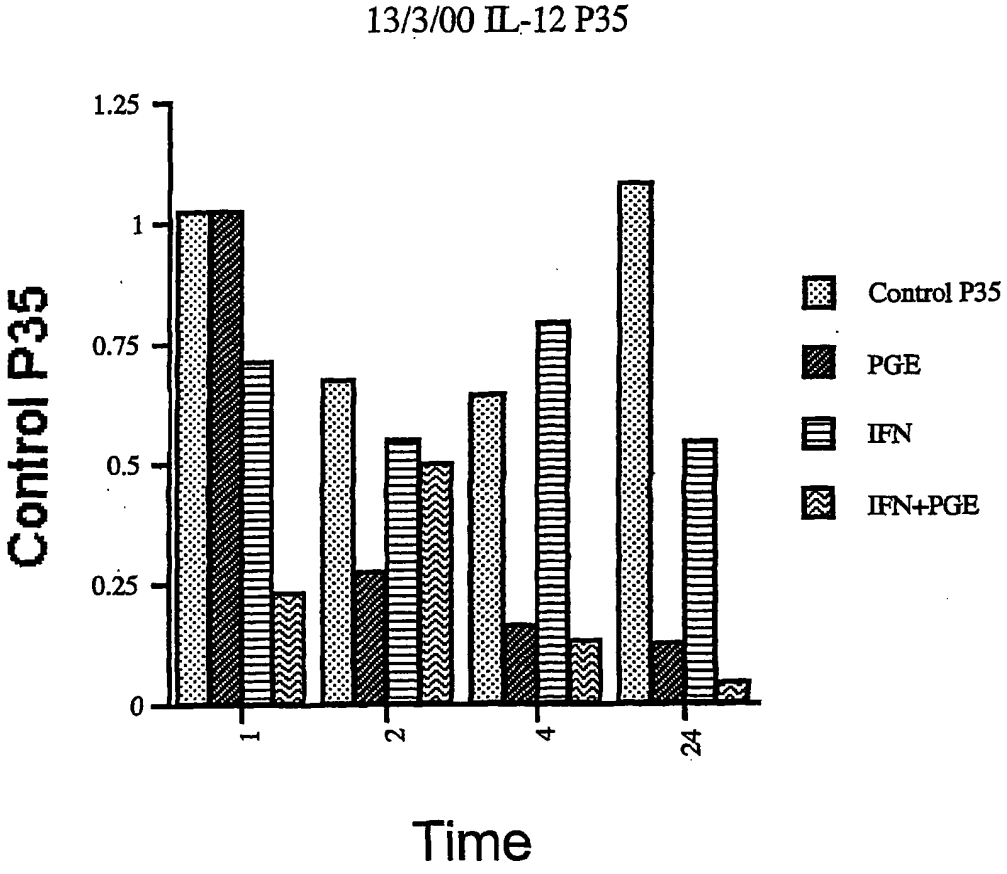
58. A therapeutic system according to Claim 57 wherein the prostaglandin is a 19-hydroxy PGE, and wherein the 19-hydroxy PGE, and optionally the type IV selective PDE inhibitor, are for administration to the bronchial tree or lungs of the patient *via* an aerosol.

59. A therapeutic system according to any one of Claims 44 to 58, wherein the tolerance to the antigen is to treat an aberrant or undesired immune response to the antigen in the patient.

60. A therapeutic system according to Claim 59 wherein the aberrant or undesired immune response involves a deficiency in IL-10 production and/or an increase in IL-12 production.

61. Any novel method of inducing tolerance to an antigen in a patient as herein described.

Figure 1A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1
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0.5
0.25
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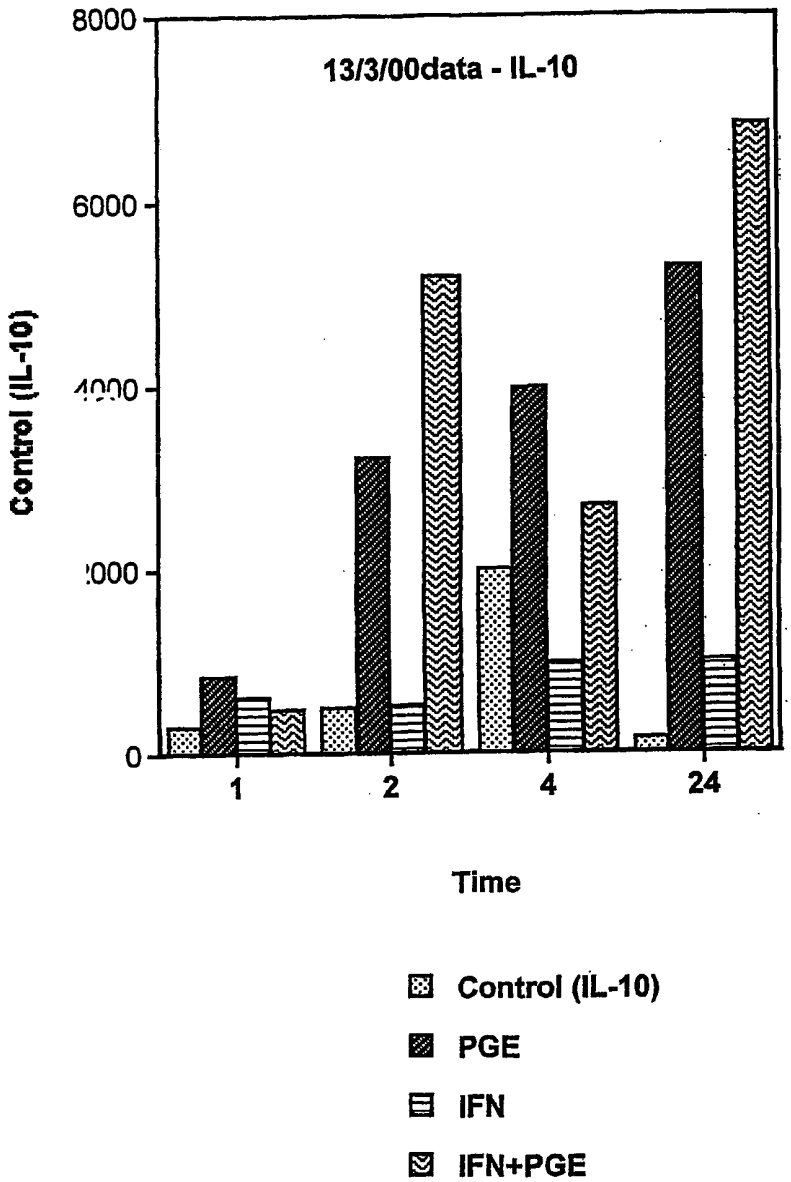
1
2
4
24
Time
Control P35
PGE
IFN
IFN+PGE

Figure 1B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2
4
24
Time
Control (IL-10)
PGE
IFN
IFN+PGE

Figure 2A

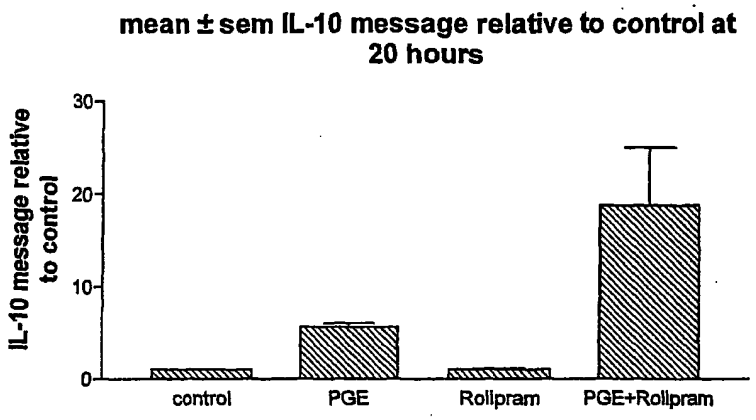


Figure 2B

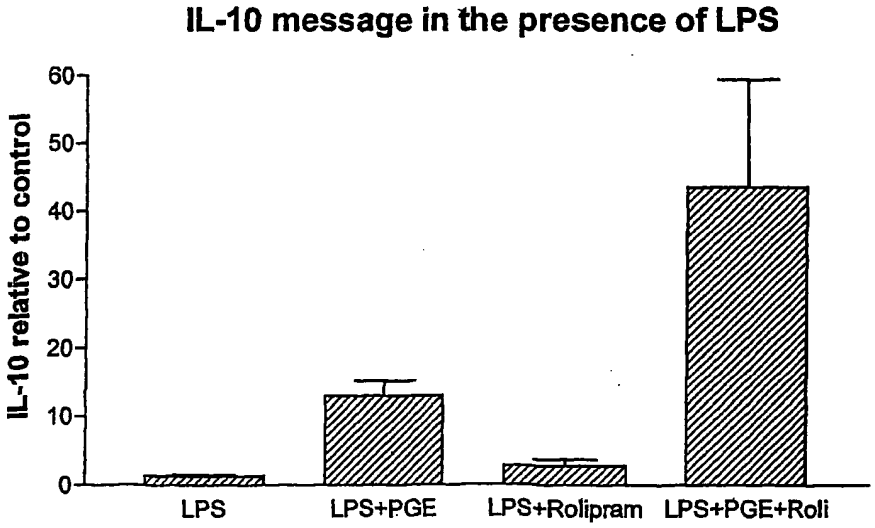


Figure 2C

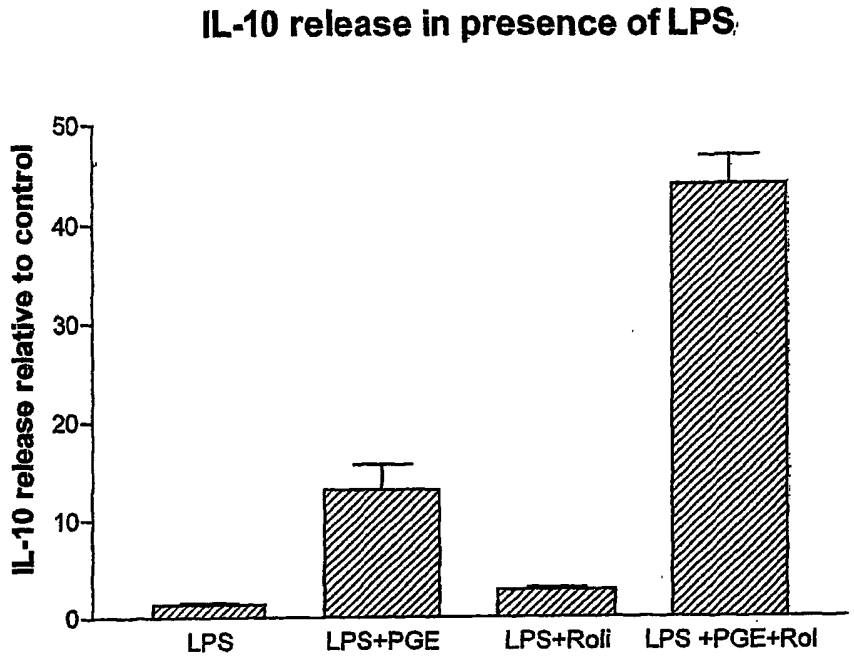


Figure 2D

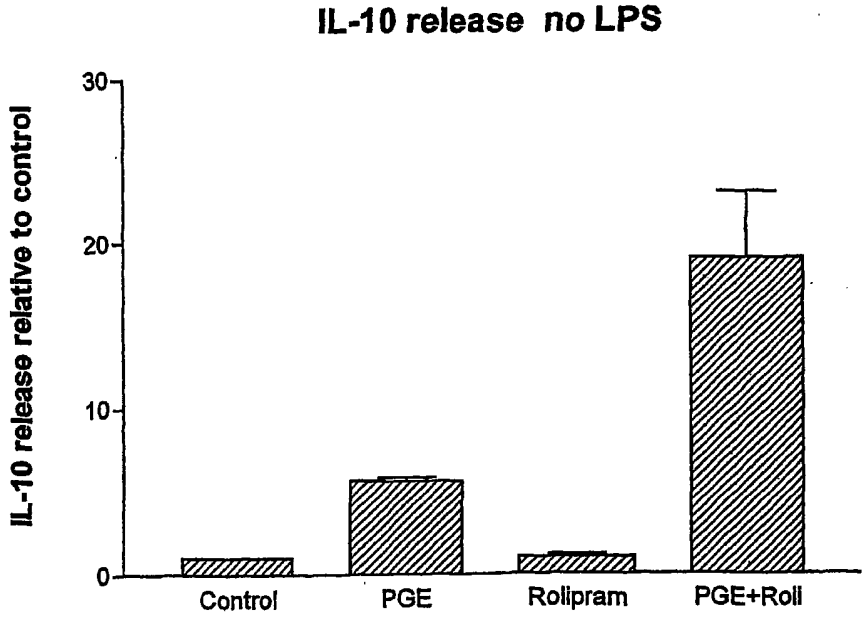
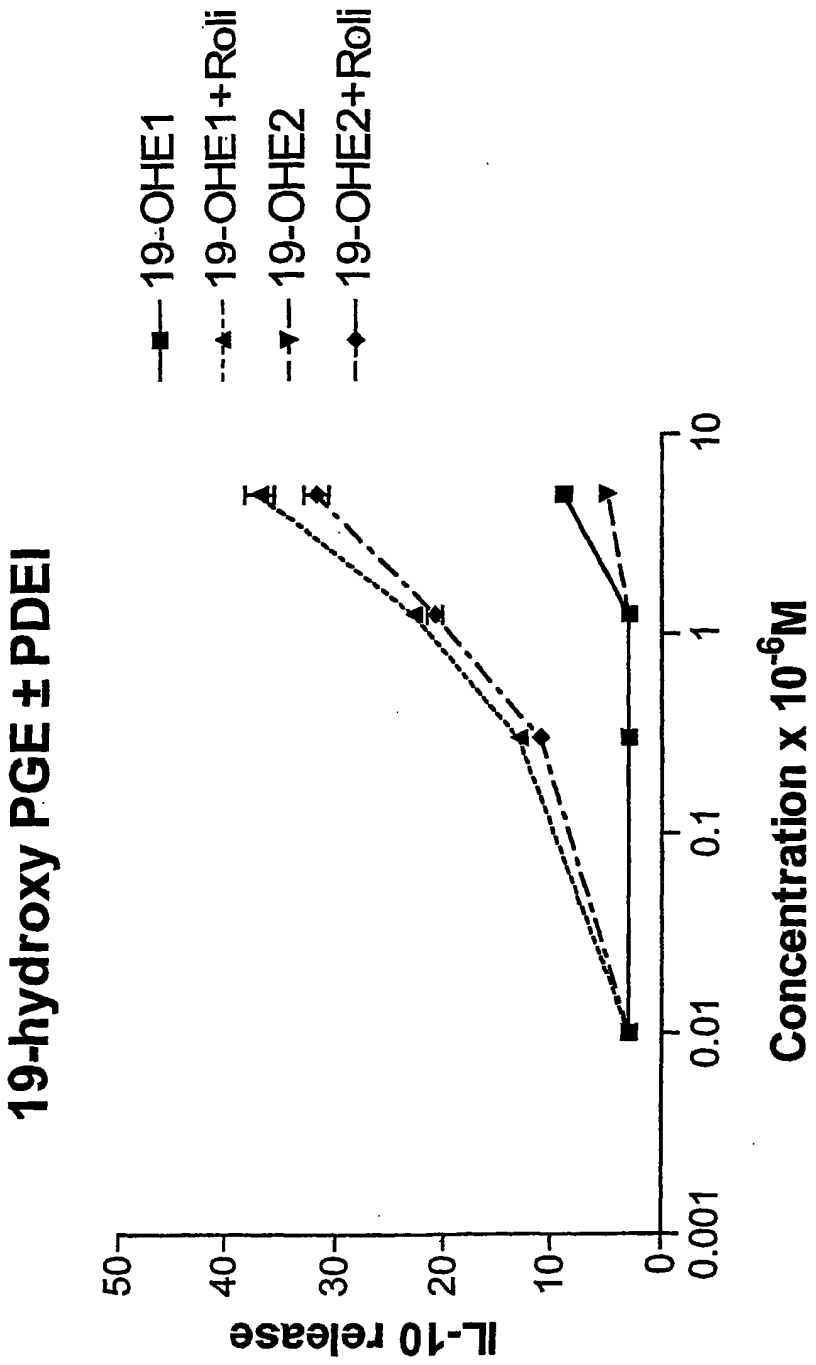


Figure 3


19-OHE1
19-OHE1+Roli
19-OHE2
19-OHE2+Roli
19-hydroxy PGE ± PDEI
IL-10 release
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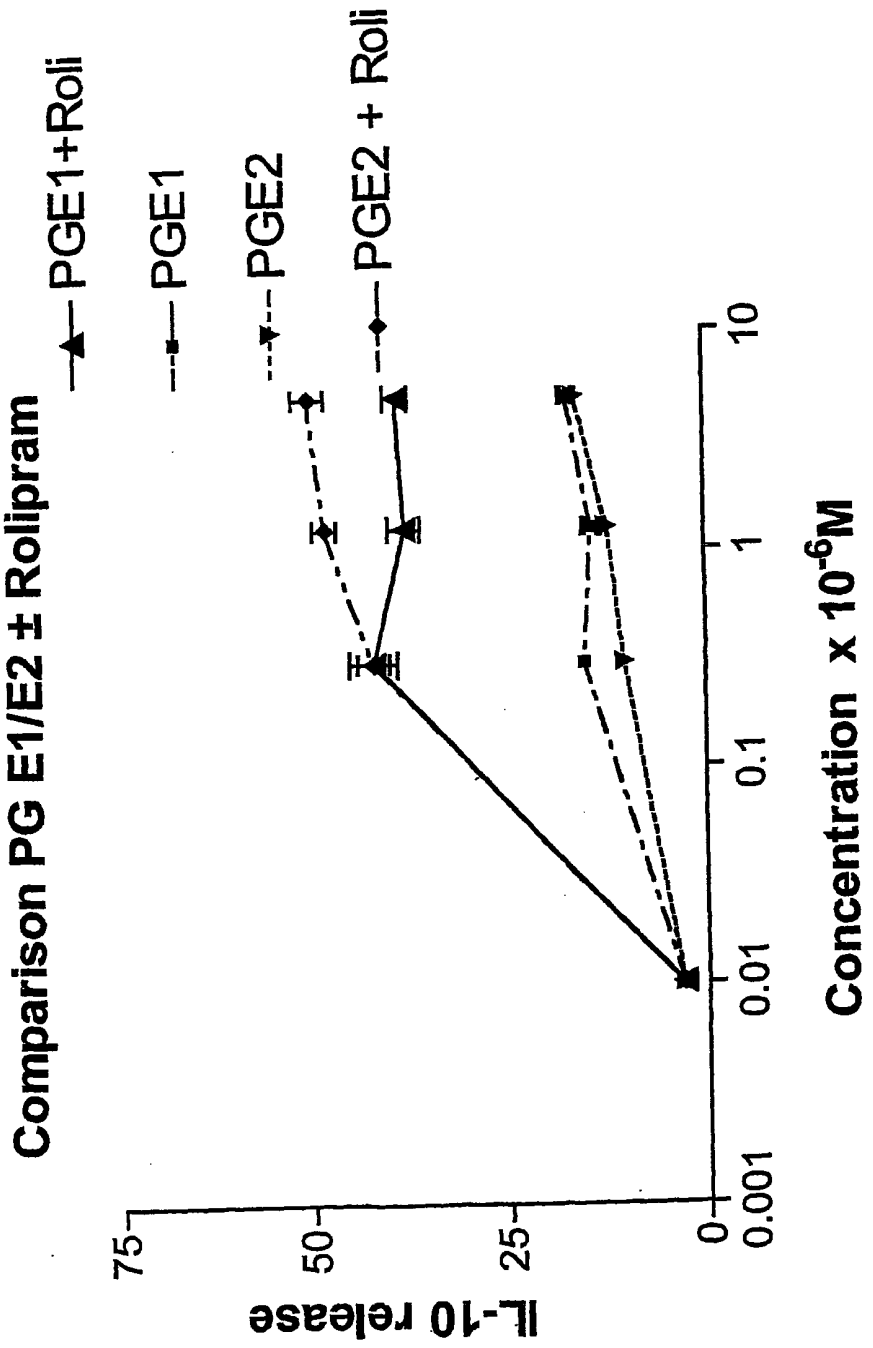
40
30
20
10
0
0.001
0.01
0.1
1
10
Concentration x 10-6M

Figure 4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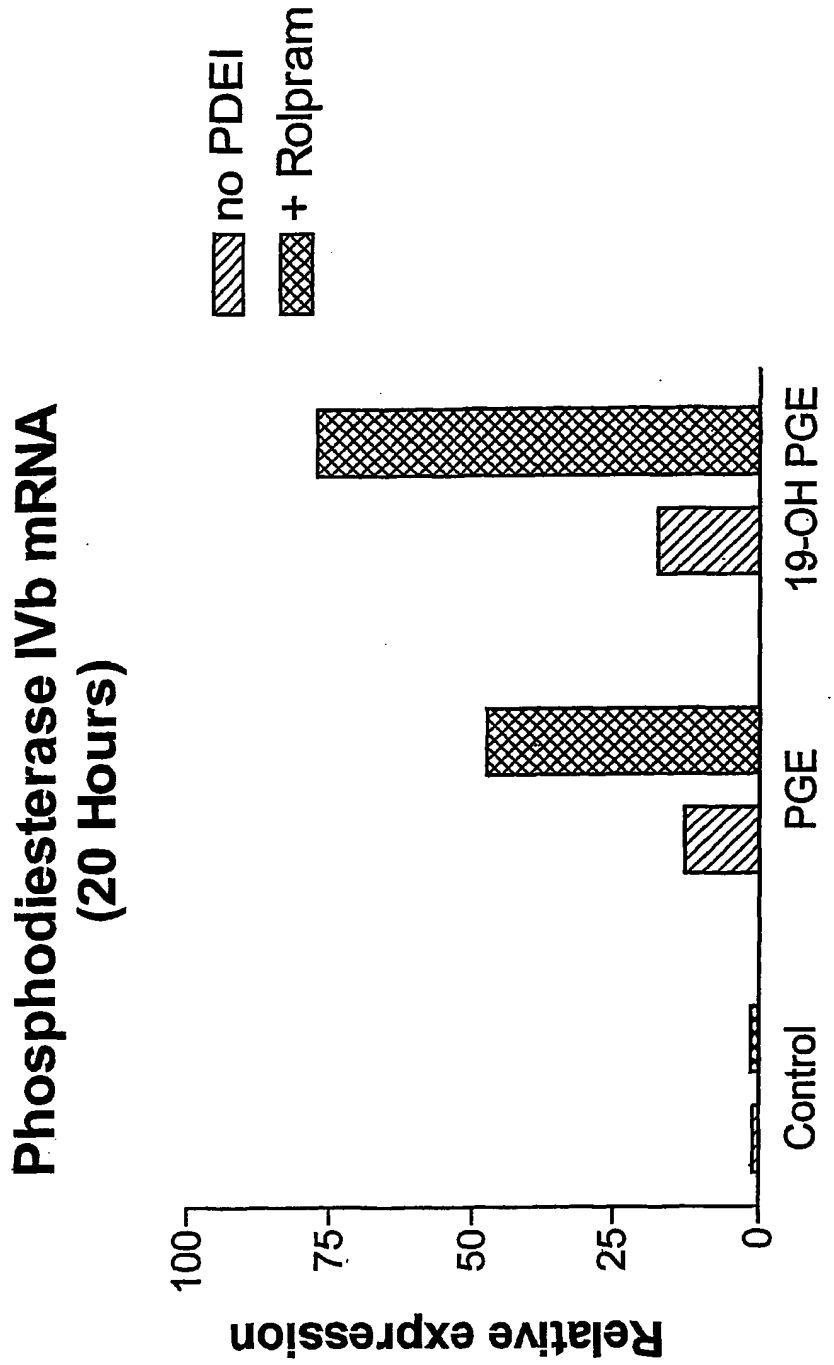
PGE1+Roli
PGE1
PGE2
PGE2 + Roli
IL-10 release
75
50
25
0
0.001
0.01
0.1
1
10
Concentration x 10-6M

Figure 5


Phosphodiesterase IVb mRNA
(20 Hours)
no PDEI
+ Rolpram
Relative expression
100
75
50
25
0
Control
PGE
19-OH PGE

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(71) Applicant *(for all designated States except US)*: **MEDICAL RESEARCH COUNCIL** [GB/GB]; 20 Park Crescent, London W1B 1AL (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **KELLY, Rodney, William** [GB/GB]; Medical Research Council Reproductive Biology Unit, University of Edinburgh, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9ET (GB).

(74) Agent: **MILES, John, S.**; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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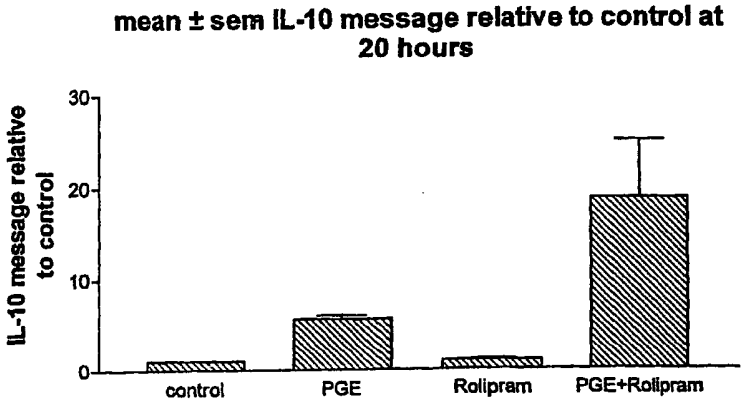
(54) Title: THERAPEUTIC METHOD FOR INDUCING TOLERANCE



(57) Abstract: A method of inducing tolerance to an antigen in a patient, the method comprising administering to the patient a prostaglandin or agonist thereof and a type IV selective phosphodiesterase (PDE) inhibitor.

WO 02/092064 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02114

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/557 A61K45/06 A61P37/06 //(A61K31/557,31:4015)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, MEDLINE, EMBASE, PASCAL, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORIUCHI, E. ET AL: "Synergistic inhibition of pannus tissue development in vitro by PGE1 plus phosphodiesterase 4 inhibitors" ARTHRITIS AND RHEUMATISM, vol. 41, no. 9, September 1998 (1998-09), page s161 XP009005530 abstract number 769	37-39, 54-56
A	DE 100 64 991 A (MERCK PATENT GMBH) 27 June 2002 (2002-06-27) the whole document	22-60
P,A	EP 1 199 074 A (WARNER LAMBERT CO) 24 April 2002 (2002-04-24) the whole document	22-60

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2003	26/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Venturini, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatiq Application No
PCT/GB 02/02114

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SOMMER N ET AL: "Therapeutic potential of phosphodiesterase type 4 inhibition in chronic autoimmune demyelinating disease" JOURNAL OF NEUROIMMUNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 79, no. 1, October 1997 (1997-10), pages 54-61, XP002113589 ISSN: 0165-5728 discussion	37-39, 54-56

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interm nal application No.
PCT/GB 02/02114

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-21,61 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/02114

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
DE 10064991	A	27-06-2002	DE	10064991 A1	27-06-2002
			AU	2636202 A	01-07-2002
			WO	0249649 A2	27-06-2002
EP 1199074	A	24-04-2002	EP	1188438 A1	20-03-2002
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			PL	349682 A1	25-03-2002
			SK	12932001 A3	04-04-2002
			US	2002119967 A1	29-08-2002

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(71) Applicant: ANDROSOLUTIONS, INC. [US/US]; 2000 Fort Sanders West Boulevard, Suite 309, Knoxville, TN 37922 (US).

(72) Inventor: NEAL, Gary, W.; 4701 Guinn Road, Knoxville, TN 37931 (US).

(74) Agent: GADIANO, Christina, M.; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Fountain Square, 11911 Freedom Drive, Reston, VA 20190 (US).

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WO 01/17479 A2

(54) Title: METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING PROSTATE DISORDERS

(57) Abstract: The present invention relates to methods, compositions, devices and kits for the prevention and treatment of prostate disorders in mammals, including, but not limited to, benign prostatic hypertrophy, carcinoma of the prostate, prostadynia, prostatitis, and chronic prostatitis. The present invention provides methods for pr eventing and treating prostate disorders in mammals by administration of a therapeutic compound to mucosal membranes in the lower urinary tract of the mammal. The present invention also provides devices for administering a therapeutic compound to mucosal membranes in the lower urinary tract of the mammal.

METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING PROSTATE DISORDERS

Field of the Invention

The present invention generally relates to novel compositions, methods, devices and kits for the prevention and/or treatment of prostate disorders in mammals. The present invention also generally relates to devices for the administration of therapeutic compounds to mucosal membranes in the lower urinary tract of mammals.

Background of the Invention

Diseases of the prostate are common maladies of male mammals, especially men. They include benign prostatic hypertrophy (BPH), carcinoma of the prostate (CaP), prostadynia, prostatitis, and chronic prostatitis.

The steadily increasing age of the world's population is a testament to the success of modern medicine and preventive care. However, this success has brought with it the problem of a greater number of men suffering from BPH, CaP and other prostate disorders.

The incidence of BPH increases steadily with age and is a nearly universal autopsy diagnosis of men in the 8th and 9th decades of their life (HA Guess, "Epidemiology and natural history of benign prostatic hyperplasia," Urol Clin North Am. 1995; 22:247-261). At least 75% of men over the age of 70 have symptoms consistent with BPH and about 30% of men may have surgery to treat BPH during their lifetime. The Baltimore Longitudinal Study of Aging found that almost 60% of men aged 60 years or older were given a clinical diagnosis of BPH (HM Arrighi et al,"Natural history of benign prostatic hyperplasia and risk of prostatectomy. The Baltimore Longitudinal Study of Aging," Urology 1991; 38 Suppl. 1:4-8). Other mammals that are known to exhibit a high incidence of BPH include dogs and Syrian Hamsters.

Carcinoma of the prostate is now the most common malignancy of men and shows the same pattern of increasing incidence with age as does BPH (SL Parker et al, "Cancer statistics," CA Cancer J Clin 1997; 45:5-27). Indeed, it has been said that every man would develop carcinoma of the prostate (CaP) if he lived long enough.

The bladder serves as a storage vessel for urine produced by the kidneys until the mammal desires to eliminate the urine by voiding. The urethra is a tube or conduit through which urine flows from the bladder to the exterior of the mammal. In man, the urethra is composed of three main divisions – the prostatic, the membranous and the penile segments (FIG. 1).

The prostate gland encases the urethra as it exits the bladder. This anatomical arrangement in which the urethra is completely surrounded by the prostate makes it susceptible to compression by the prostate. Any encroachment upon the lumen of the prostatic urethra will result in obstruction to the flow of urine.

BPH causes obstruction to the flow of urine by two major mechanisms that are distinct components – a static (fixed) component due to the hypertrophied prostate tissue and a dynamic component due to excessive tone in the smooth muscle tissues of the prostate. Both of these mechanisms cause compression and obstruction of the urinary outflow tract. The pathophysiology of BPH involves hypertrophy of the glandular and stromal tissue of the peripheral zone of the prostate and the periurethral area that surrounds the urethra (see FIG. 2) leading to narrowing of the lumen and mechanical obstruction of the urinary outflow tract. Pathology findings on prostate tissue from patients with BPH include fibrosis and hyperplasia of the musculature and gland structure of the prostate.

Patients with BPH commonly complain of symptoms that include difficulty initiating urination (hesitancy), difficulty terminating urination (dribbling), frequent urination secondary to an inability to completely empty the bladder of urine (frequency) and having to awaken in the night to empty the bladder (nocturia). Since no methods are known to prevent or cure BPH, the primary focus of treating BPH is to alleviate these complaints and thereby improve the patient's quality of life.

Two measures of the degree of outflow tract obstruction that are commonly followed in studies of patients with BPH are the subjective complaints of BPH symptoms and measures of the ability to empty the bladder of urine (urodynamics). Urodynamics studies consist of measuring the rate of urine flow and the quantity of urine produced as the patient urinates into a container placed on an electronic scale. A graph of urine flow versus time is produced and the patient's urine flow measurements may then be compared to population derived average urine flow measurements. More complex urodynamics studies measure pressures produced by contraction of the bladder muscles during urination. One measure of the degree of urinary tract obstruction is the maximum or peak urinary flow rate as measured by urodynamics studies. FIG. 3 shows typical urodynamics studies. Peak urinary flow rates of less than 15 milliliters (mls) per second indicate significant urinary obstruction and flow rates of less than 5 mls/second are felt to be an indication for prompt surgical relief of the obstruction.

Prostate specific antigen (PSA) is a serum protease that is widely used as an indicator of disease severity in both BPH and CaP. Not only are prostatic tissues the only source of PSA but serum PSA levels closely correlate with the total amount of prostate tissue present in the body at

any given time. Treatments that reduce the tumor mass in CaP or that induce regression of BPH will demonstrate a reduction in serum levels of PSA.

Current medical treatments of BPH include surgery; systemic therapy with alpha-adrenergic blocking agents such as doxazosin, terazosin, prazosin, alfuzosin, R(+)-terazosin, bunazosin, indoramin and tamulosin; alteration of testosterone metabolism; and therapy with an oral herbal medicine extracted from the saw palmetto (Serenoa repens). Huff (US Pat. No. 5,760,054) discloses a number of more specific alpha 1C adrenergic receptor antagonists that may be utilized in the treatment of BPH.

Treatment of BPH with alpha-adrenergic blocking agents is believed to exert beneficial effects by reducing the adrenergic tone of the smooth muscle cells in the prostate via the alpha-1 receptors. Excessive alpha adrenergic tone in the prostatic smooth muscle cells results in a reversible narrowing of the diameter of the urinary outflow tract as it courses through the prostate. This dynamic component of BPH is believed to be the pathophysiology of BPH in men with small prostates. Oral administration of alpha blockers leading to decreased alpha-1 adrenergic tone is felt to result in relaxation of prostatic smooth muscle with a resultant functional improvement in obstructive urinary tract symptoms such as hesitation, dribbling and nocturia. Alpha-adrenergic blocking agents are therefore best used in men with small prostates where smooth muscle contraction is likely to be the primary contributor to the obstructive symptoms. A meta-analysis of placebo-controlled studies of alpha blockers shows improvement in the peak urinary flow rates by 1.5 ml/sec (LM Eri et al, "Alpha-blockade in the treatment of symptomatic benign prostatic hypertrophy," J Urol 1995; 154:923-934).

Another approach taken in the medical treatment of BPH involves altering the metabolism of testosterone. Testosterone is converted by 5alpha-reductase into dihydrotestosterone, a compound that stimulates tissue growth in the prostate. This enzyme exists in at least two isoenzyme forms, Type I and Type II. For reasons that are not known, the ratio of dihydrotestosterone to testosterone present in the blood increases with age. The conversion to dihydrotestosterone greatly increases the potency of testosterone in many tissues including the prostate. The growth of the prostate tissue in BPH is exacerbated by the increased ratio of dihydrotestosterone to testosterone that accompanies aging. Finasteride is a drug specifically developed to block the reduction of testosterone to dihydrotestosterone by 5alpha-reductase. Oral administration of finasteride is approved by the FDA as a treatment for the symptoms of BPH. Finasteride has a gradual onset of action resulting in a 70% reduction in serum dihydrotestosterone levels after daily dosing with 5 milligrams. Administration of finasteride for a period of 6-12 months is generally necessary to determine whether a patient with

BPH will improve. Unfortunately, a minority of all patients with BPH improve on oral finasteride and the degree of improvement is relatively small. For example, two large clinical studies demonstrated an increase of only ~ 1.6 mls/second in peak urinary flow rates with finasteride treatment. Meta-analysis of studies with finasteride demonstrate a 0.5 to 0.8 ml/sec average improvement in peak urinary flow rates compared to placebo (LM Eri et al," Treatment of benign prostatic hyperplasia. A pharmacoeconomic perspective," Drugs Aging 1997 Feb; 10(2):107-18).

Another option that may be suggested for men with BPH is an oral herbal medicine preparation extracted from the saw palmetto (Serenoa repens). This preparation contains a variety of compounds that bind androgen receptors and demonstrate 5alpha-reductase inhibition in vitro. The mechanism of action is complex and may involve other pharmacologic activities. Several clinical studies indicate that extracts of Serenoa repens exhibit roughly the same amount of clinical symptom improvement and improvement in peak urinary flow as does finasteride (GS Gerber, "Saw Palmetto in men with lower urinary tract symptoms:effects on urodynamic parameters and voiding symptoms," Urology 1998 Jun; 51(6):1003-7).

Each of these treatments has limitations and drawbacks. Most of the side effects of medical treatments stem from the systemic (oral) administration of a therapeutic agent to treat a very localized problem in the prostate. The alpha-adrenergic receptor antagonists may cause a significant decrease in the systolic blood pressure, syncope, orthostatic hypotension, asthenia, dizziness, headache, sleepiness, fatigue and impotence. A recent myocardial infarction, transient ischemic attack or cerebrovascular accident constitute relative contraindications to the use of alpha-blockers. The effect of alpha-blockers is usually apparent in the first two weeks of treatment and maximum clinical effects are seen in one or two months (LM Eri et al, Drugs Aging, op cit). Side effects of finasteride administration in men are primarily sexual – erectile dysfunction, decreased volume of ejaculate and loss of libido. Severe teratogenic effects on the fetus preclude the use of finasteride by men whose partner may conceive. Side effects of Serenoa repens therapy are generally the same as with finasteride.

The use of oral therapeutic compounds leads to exposure of all the tissues of the body in an attempt to reach the prostate gland. Local administration of a drug directly to the prostate is hampered by the fact that the prostate gland is an internal organ. The applicant believes that local therapy of the prostate has been achieved to date only by injection of drugs via a hypodermic needle directly into the prostate (A Morales, "Intralesional administration of biological response modifiers in the treatment of localized cancer of the prostate: a feasibility

study," Urology 1997; 50(4): 495-502). This method of administration is difficult, painful and potentially dangerous.

Administration of therapeutic compounds systemically also has severe drawbacks. Doses in systemic administration are much greater than one might otherwise need if a more direct route of administering drugs were possible. For example, a 40 gram prostate gland in an 82 kilogram (180.4 pounds) man constitutes only 0.05% of the total body mass. Thus, systemic therapy must expose 99.95% of the body to a pharmacologically active drug in order to reach therapeutic levels in the 0.05% of the targeted prostate tissue. Alpha receptors are present diffusely throughout the vascular system and in other organs of mammals. Thus, drugs given to block alpha receptors in the prostate will certainly result in inhibiting normal alpha receptor mediated physiologic functions throughout a mammal. Dihydrotestosterone exerts effects upon most tissues and organs in a male mammal. Thus, reductions in 5alpha-reductase activity systemically must result in other than the desired effects upon the growth of prostatic tissue. Administration of systemic therapy in order to treat the prostate is roughly analogous to painting a house in order to paint the window frame or to spraying a city with pesticides in order to eliminate insects in the city gardens.

Surgical treatment of BPH is the most common surgery of men in the developed countries of the world. In 1989, 400,000 men in the US underwent surgery of the prostate at a cost of greater than $3 billion (MA Kortt et al "The economics of benign prostatic hyperplasia treatment: a literature review," Clinical Therapeutics 1996; 18(6):1227-1241). The most common prostate surgery involves trans-urethral resection of the prostate (TURP), which is accomplished by resecting the prostatic tissues surrounding the urethra that cause obstruction through a large bore urinary catheter. One prospective randomized study of TURP demonstrated an increase in peak urinary flow of 7.0 ml/sec after surgery (RS Cowles et al "A prospective randomized comparison of TURP to visual laser ablation of the prostate for the treatment of benign prostatic hypertrophy," Urology 1995 Aug; 46(2):155-600). A second multicenter study demonstrated an increase of 11.35 ml/sec (130%) in peak urinary flow rates following TURP. TURP gives a 4 – 8 times greater increase in peak urinary flow rates than does treatment with alpha blockers and a 9 – 22 times greater increase in peak urinary flow rate when compared to finasteride. This surgical procedure carries the usual attendant health risks of a major operation in addition to the complications of urinary incontinence and impotence. Approximately 15% of patients undergoing TURP are estimated to have serious complications and about 5% require a repeat operation after two years. (LM Eri et al, Drugs Aging, op cit). These limitations have spurred the development of a number of other approaches to remove the obstructing tissues with

fewer complications such as microwave ablation, cryotherapeutic ablation and laser ablation of the prostate (see M Barba et al,"New technologies in transurethral resection of the prostate," Curr Opin Urol 2000 Jan; 10(1):9-14; A Koritt op cit and U.S. Pat. No. 6,102,929 as examples). Each new procedure has its individual complications and none has supplanted TURP. The applicant is unaware of any method presently available of treating BPH that can replace surgical removal of the excess prostatic tissue much less prevent the nearly universal development of BPH in aging men.

Thus, there is a pressing need for new and improved methods, compositions and devices to prevent and treat prostate disorders in mammals. Compositions and methods of treatment that exhibit more rapid onset of action, more potent effects on peak urinary flow rates, less systemic side effects, without deleterious effects upon sexual function or urinary continence are needed. Since aging is also associated with increasing incidences of heart attack and strokes, methods of treating BPH that do not exacerbate cardiovascular or cerebrovascular disease are particularly needed. There is also a need for routes of administration for drugs that minimize systemic exposure. There remains a need for compositions and kits useful for preventing and treating prostate disorders in mammals.

Summary of the Invention

It is one object of the present invention to provide compositions for effectively preventing and/or treating prostate disorders in mammals.

It is another object of the present invention to provide methods for preventing and/or treating prostate disorders in mammals.

It is another object of the present invention to provide devices to deliver therapeutic compounds to the mucosal membranes of the lower urinary tract.

It is another object of the present invention to provide kits for preventing and/or treating prostate disorders in mammals.

These objects have been obtained by the inventor's discovery that administering certain therapeutic compounds to mucosal membranes of the lower urinary tract of a mammal is effective in preventing and/or treating prostate disorders.

The present invention has demonstrated a method of treating BPH with efficacy within one hour of treatment, a surprisingly rapid response compared to weeks or months needed to demonstrate efficacy with present therapies. Further, one treatment has normalized urinary flow in some patients given this therapy. In several cases, the present invention has given improvement in urinary flow rates that exceed reports of improvement with surgery. This

invention involves minimal intervention when compared to present therapies and offers hope for the prevention and/or treatment of prostate disorders.

Additional aspects, features, embodiments and advantages of the present invention will be set forth, in part, in the description that follows, or may be learned from practicing or using the present invention. The objects and advantages may be realized and attained by means of the features and combinations particularly pointed out throughout this description and the appended claims. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not to be viewed as being restrictive of the invention as claimed.

Brief Description of the Drawings

The accompanying drawings, which are incorporated in, and constitute a part of, this specification, illustrate embodiments of the present invention and, together with the description, serve to exemplify the principles of the present invention.

FIG. 1 depicts the anatomy of the male urethra.

FIG. 2 depicts the anatomical zones of the male prostate.

FIG. 3 depicts voiding urodynamics studies.

FIG. 4 depicts a method of administration of therapeutic agents via the prostatic urethra.

FIG. 5 depicts novel devices for administration of therapeutic agents to the mucosal membranes of the lower urinary tract in mammals.

Detailed Description of the Preferred Embodiments

All patents, patent applications and publications cited in this description are incorporated here by reference in their entirety.

Thus, in a first embodiment, the present invention provides novel compositions for the prevention and/or treatment of prostate disorders in mammals.

As used herein, "prostate disorders" refers to benign prostatic hypertrophy (BPH), carcinoma of the prostate (CaP), prostadynia, prostatitis, and chronic prostatitis.

One novel composition comprises a prostaglandin compound and an interferon. Another novel composition comprises meatal suppositories with tocopherol analogs and/or vitamin C analogs. Meatal suppositories containing leuprolide acetate, finasteride and verapamil in a free base form are also believed to be novel.

In a second embodiment, the present invention provides novel methods for the prevention and/or treatment of prostate disorders in mammals comprising administration of one or more therapeutic compounds to the mucosal membrane of the lower urinary tract of the mammal.

In a preferred embodiment, the method for preventing prostate disorders comprises:

a. Identifying the population of mammals at risk of developing a prostate disorder;

b. Performing baseline testing of mammals at risk;

c. Administering one or more therapeutic compound(s) to the mucosal membrane of the lower urinary tract of the mammal; and

d. Repeating the baseline testing to evaluate the mammal's response to intervention and to determine whether subsequent interventions should be altered.

When the prostate disorder is BPH, mammals at risk of BPH can be identified (step a) by, for example, evaluating historical factors known to be associated with BPH such as age, race, family history and history of exposure to androgens. Since the strongest factor associated with BPH is age, one may consider every man over a certain age such as 40 to be at risk of developing BPH and a candidate for preventative therapy.

After identifying mammals with BPH, baseline testing (step b) can be performed on, for example, serum PSA, testosterone and dihydrotestosterone levels. A screening urodynamics study with a minimum of peak and mean urinary flow rates can also be performed. Assessment of prostate size by digital exam, ultrasonography, computed tomography or by magnetic resonance imaging may also be used for baseline testing. Symptomatology is determined according to the American Urological Association Symptom Index by inquiring about and recording the following 7 symptoms: sensation of not having emptied the bladder completely after urination; having to urinate again in less than 2 hours after urinating; having to stop and start again several times during urination; difficulties in postponing urination; weak urinary stream; having to push or strain to begin urination; and having to get up at night to urinate (MJ Barry et al "The measurement committee of the American Urological Association..." J Urol 1992; 148:1549-57).

After conducting the baseline tests, one or more therapeutic compound(s) may be administered to the mucosal membrane of the lower urinary tract of the mammal (step c), preferably utilizing the least invasive method possible. For example, meatal suppositories containing (a) PGEs with or without interferons or (b) 5alpha-reductase inhibitors such as fatty acids, extracts of Serenoa repens or finasteride are suitable for administration. Administration of a suitable dose of the therapeutic agent nightly or every other night is also suitable.

After completing administration of the desired dosage regimen, repeat baseline testing to evaluate the mammal's response to intervention and to determine whether subsequent interventions should be altered (step d) can optionally be carried out by re-evaluating the baseline determinants recorded in step b at intervals of 6 months to 2 years. These determinants preferably consist of at least the symptomatology, the peak urinary flow rate and the PSA level. Improvement in these determinants is desirable and indicates regression of the BPH. Continuation of the intervention used is preferable. Should the individual be without symptoms and possess a normal PSA and Peak flow rate, further improvement in an otherwise normal individual may not be possible. One indication that the intervention used is effective is no progressive increase in PSA, decrease in peak urinary flow or development of symptomatology occurs. In this case, the individual should continue the intervention and be re-evaluated in 6 month to 2 years. If worsening of the symptoms or other indicators occurs, use of higher doses of therapeutic compound(s) may be tried.

When the prostate disorder is CaP, mammals at risk of developing CaP can be identified (step a) by analysis of factors including, but not limited to, family history, race and age. Strongly positive family histories or pathology reports of pre-malignant changes on prostate tissue are indications to initiate preventative therapy. Advanced age is also a strong risk factor for CaP.

After identifying mammals at risk of developing CaP, baseline testing (step b), such as serum PSA and assessment of prostate size by digital exam, ultrasonography, computed tomography or by magnetic resonance imaging may be performed. Available prostate biopsy reports can be studied and new prostate biopsy material obtained at the discretion of the clinician.

After performing baseline testing, one or more therapeutic compound(s) may be administered to the mucosal membrane of the lower urinary tract of the mammal (step c). For example, use of meatal suppositories with (a) prostaglandins with or without an interferon of the alpha or gamma subgroup or (b) tocopherols, vitamin C or retinol or their analogs are suitable for administration to the mammal. Preferably, the prostaglandin is PGA-1, PGA-2, PGJ2, Δ^{12}-PGJ-2, 15-deoxy-$\Delta^{12,14}$-PGJ-2, PGD-2 or 15-deoxy-$\Delta^{12,14}$-PGD-2. The therapeutic compound(s) can be administered nightly or every other night.

After completing the administration of the desired dosage regimen, baseline testing for CaP (step d) can be accomplished, for example, by serial PSA determinations or by repeat prostate biopsy.

Methods for treating BPH and CaP preferably comprise

a. Diagnosing the mammal as having BPH;

b. Performing baseline testing of the mammal having BPH;

c. Administering one or more therapeutic compound(s) to the mucosal membrane of the lower urinary tract of the mammal; and

d. Performing baseline testing to evaluate the mammal's response to the treatment and to determine whether subsequent treatments should be altered.

Performing baseline testing of the mammal and administration of the therapeutic compound(s) are preferably accomplished by the same measures described above in connection with methods for preventing BPH, if the condition is mild. More severe cases of BPH are best treated by administration of one or more therapeutic compound(s) to the prostatic urethra as described below and in the examples. Treatment of local CaP may be effected by administration of chemotherapeutic agents via the prostatic urethra.

As used herein, "therapeutic compound" refers to any therapeutic compound of benefit or potential benefit to prostate disorders. Particularly preferred therapeutic compounds are selected from any of the groups listed below for which non-limiting examples are given:

I. Autocoids and Cytokines such as Prostaglandins and Interferons

II. Chemotherapeutic Agents

III. Alpha-receptor antagonists

IV. Prostaglandin dehydrogenase inhibitors

V. Phosphodiesterase inhibitors

VI. Anticholinergic/antispasmodic agents

VII. Anti-Androgens

I. <u>Cytokines</u>

I (A). <u>Prostaglandins</u>

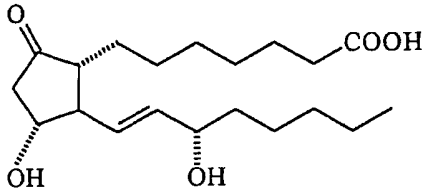
Examples of suitable prostaglandins include any natural or synthetic chemical designated to belong to a prostaglandin family, such as PGE-1; PGE-2; PGE-3; PGA-1; PGB-1; PGD-2; 15-deoxy-$\Delta^{12,14}$-PGD-2, PGE-M; PGF-M; PGH-2; PGI-2; 19-hydroxy-PGA-1; 19-hydroxy-PGB-1; PGA-2; PGB-2; 19-hydroxy-PGA-2; 19-hydroxy-PGB-2; PGB-3; 16,16-dimethyl-PGE-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; 16,16-dimethyl-PGE-2; 11-deoxy-15-methyl-PGE-1; 16-methyl-18,18,19,19-tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; (+)-4,5-didehydro-16-phenoxy-tetranor-PGE-2 methyl ester; 11-deoxy-11a,16,16-trimethyl-PGE-2; (+)-11a,16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-trans-prostene; 9-chloro-16,16-dimethyl-PGE-2; arboprostil; iloprost; CL 115,347;

16,16-dimethyl-PGE-2; 15(S)-15-methyl-PGE-2; 9-deoxy-9-methylene-16,16-dimethyl-PGE-2, potassium salt; carbaprostacyclin; prostaglandin D-2; 19(R)-hydroxy-PGE-2; 13,14-dihydro-PGE-1; 11β-PGE-2; 19(R)-hydroxy-PGE-1; 11-deoxy-16,16-dimethyl-PGE-2; PGJ-2; Δ^{12}-PGJ-2; 15-deoxy-$\Delta^{12,14}$-PGJ-2 and semisynthetic or synthetic derivatives of these natural prostaglandins. Cyclodextrin complexes are also included as they may enhance the activity of the solution and stabilize the prostaglandin. Racemic, optically enriched or purified stereoisomers of any of these compounds are also included. Physiologically acceptable salts are also included.

Preferably, the prostaglandin is PGE-1, PGE-2, PGE-3, misoprostol or misoprostanoic acid for the treatment and prevention of BPH. Preferably, the prostaglandin is PGA-1, PGA-2, PGJ2, Δ^{12}-PGJ-2, 15-deoxy-$\Delta^{12,14}$-PGJ-2, PGD-2 or 15-deoxy-$\Delta^{12,14}$-PGD-2 for the treatment and prevention of prostate cancer.

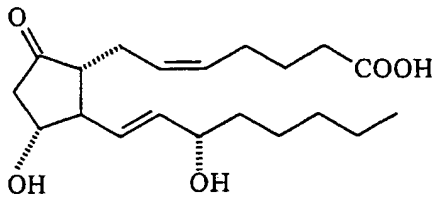
Such prostaglandins are commercially available from Cayman Chemical, Ann Arbor MI or described in Alex Gringanz, Introduction to Medicinal Chemistry, Wiley-VCH, Inc., New York, pp. 158-159 and 641-642, 1997, which is incorporated herein by reference.

PGE-1, prostaglandin E_1, is also known as alprostadil or PGE_1. The formal chemical name of PGE-1 is 3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentaneheptanoic acid, and the structure of PGE-1 is



Prostaglandin E_1 may be isolated from sheep seminal vesicle tissue as described in Bergstrom et al., Acta. Chem. Scand., vol. 16, p. 501 (1962) and J. Biol. Chem., vol. 238, p. 3555 (1963). The synthesis of prostaglandin E_1 may be carried out as described in Corey et al., J. Am. Chem. Soc., vol. 91, p. 535 (1969); Corey et al., J. Am. Chem. Soc., vol. 92, p. 2586 (1970); Sih et al, J. Am. Chem. Soc., vol. 94, p. 3643 (1972); Sih et al., J. Am. Chem. Soc., vol. 95, p. 1676 (1973); Schaaf et al., J. Org. Chem., vol. 37, p. 2921 (1974); and Slates et al., Tetrahedron, vol. 30, p. 819 (1974).

PGE-2, prostaglandin E_2, is also known as dinoprostone or PGE_2. The formal chemical name of PGE-2 is 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid, and the structure of PGE-2 is:



Prostaglandin E_2 may be isolated from sheep seminal vesicle tissue as described in Bergstrom et al., Acta. Chem. Scand., vol. 16, p. 501 (1962). Prostaglandin E_2 may be synthesized as described in Corey et al., J. Am. Chem. Soc., vol 92, p. 397 (1970); Corey et al., J. Am. Chem. Soc., vol. 92, p. 2586 (1970); and Heather et al., Tetrahedron Letters, p. 2313 (1973).

PGE-2 is also commercially available as a Prostin E-2 ™suppository and as Prepidil Gel™ from Pharmacia & UpJohn Company, Kalamazoo, MI, and as Cervidil™ from Forest Pharmaceuticals, Inc., St. Louis, MO. These preparations are indicated for cervical ripening and contain between 0.5 and 20 mgs of PGE-2.

Misoprostol, also known as 15-Deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester, has the formal chemical name of ( )-methyl-(1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate. Misoprostol (15-Deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester) may be prepared as described in U.S. Pat. No. 3,965,143.

Enprostil has the formal chemical name of [1∀,2∃(1E,3R*),3∀]-7-[3-hydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)-5-oxocyclopentyl]-4,5-heptadienoic acid methyl ester. Enprostil may be prepared as described in U.S. Pat. No. 4,178,457.

I (B). Interferons

Interferons are a diverse group of naturally occurring cytokines and immunomodulatory polypeptide agents. Certain interferons are known to exhibit chemotherapeutic effects against certain malignancies, immunosuppressive effects, antiviral effects or antiproliferative effects. Several of this group have been produced by recombinant technology. Interferon alpha-2b from Schering Corporation (Intron A™), interferon alpha-2a from Roche Laboratories (Roferon-A™), interferon beta-1b from Berlex Laboratories (Betaseron™) and interferon gamma-1b (Actimmune™) from Genentech are commercially available agents.

Examples of suitable interferons for use in the present invention include interferon alpha, interferon beta or interferon gamma of natural or synthetic origin that exhibit scar lysis. Specific preferred interferons for use with this invention include any interferon that exhibits the ability to reduce or inhibit the production of fibrous connective tissue, including, but not limited to,

interferons of the alpha and gamma sub-groups are preferred. Examples include interferon alpha-2a, interferon alpha-2b and interferon gamma-1b.

II. Chemotherapeutic Agents

Any available chemotherapeutic agents that show activity against prostate carcinoma may be used in the present invention. Agents that demonstrate marked irritation or toxicity to the mucosal surface are to be avoided. Several relatively innocuous agents that demonstrate in vitro activity against CaP cell cultures are readily administered by the present method such as, but not limited to, tocopherols, alpha-tocopherol succinate, vitamin C and analogs, retinol and vitamin A analogs (C Maramag et al "Effect of vitamin C on prostate cancer cells in vitro: effect on cell number, viability and DNA synthesis" Prostate 1997 Aug 1; 32(3): 188-95).

Szarka reviews the strategy of chemoprevention as a possible method of blocking the development of cancers in humans (CF Szarka et al "Chemoprevention of cancer" Curr Probl Cancer 1994 Jan-Feb;18(1):6-79). These strategies center around the systemic administration of agents that have been shown to inhibit the growth of cancer cells in culture. The present invention makes it possible to deliver to the urinary tract sufficient amounts of tocopherols and vitamin C analogs to reach the necessary concentrations demonstrated by the in vitro studies. Systemic administration of these agents does not allow the delivery of sufficient tissue concentrations to be effective. Concentrations of 1 – 2 millimolar for ascorbic acid (vitamin C), 0.5 millimolar for alpha-tocopherol and 10 micromolar for alpha-tocopherol succinate are necessary to demonstrate cytostatic or cytotoxic effects on cancer cell cultures. These tantalizing reports must be balanced by the observation that the minimal target tissue concentrations necessary to suppress the development of cancer cells or to kill cancer cells already present in a mammal exceed the maximum levels possible in oral administration by a factor of 10 – 20 fold for ascorbic acid and by around 7 – 10 fold for tocopherol. The most potent of these agents is alpha-tocopherol succinate, a succinic acid ester of tocopherol commonly used as a "dry" or solid form of vitamin E in supplements. Oral administration of this most potent antineoplastic agent results in undetectable levels of alpha-tocopherol succinate available systemically due to the rapid hydrolysis of this compound by ubiquitous serum and tissue esterases into alpha-tocopherol and the resultant 50 fold reduction in potency. Suppositories made in Example 8 are 45 mM in alpha-tocopherol succinate or 640 fold greater than the minimally effective concentration. No esterases separate the suppositories from cancerous lesions in the bladder. The present method may be used with any agent that exhibits inhibitory or toxic activity towards cancer cells but is tolerated by normal mucosal cells.

III. Alpha-Receptor Antagonists

Alpha-receptor antagonists including, but not limited to, prazosin, phentolamine, phenoxybenzamine, dibenzamine, doxazosin, terazosin, trimazosin, tolazoline, corynthanine, rauwolscine, tamsulosin and piperoxan, are suitable for use in the present invention.

IV. Prostaglandin Dehydrogenase Inhibitors

By the term "prostaglandin dehydrogenase inhibitor" it is meant any compound which exhibits a significant and selective inhibition of prostaglandin degrading enzyme, or 15-hydroxyprostaglandin dehydrogenase (PGDH). Two forms of 15-hydroxyprostaglandin dehydrogenase (PGDH) are known: Type I, which is NAD^+ dependent, and Type II, which is $NADP^+$ dependent. Type I operates at a Km one order of magnitude lower than Type II and is thus more significant physiologically. Type I PGDH is described in Mak et al, Biochimica et Biophysica Acta, vol. 1035, pp. 190-196 (1990); Ensor et al, J. Lipid Mediators Cell Signalling, vol. 12, pp. 313-319 (1995); and Berry et al, Biochemical Pharmacology. vol. 32, no. 19, pp. 2863-2871 (1983), which are incorporated herein by reference. Berry et al., Tai et al., Muramatsu et al., and Mak et al. describe assays for determining enzymatic activity of Type I PGDH as well as methods for determining the degree of inhibition of this enzyme.

Type II PGDH is described in Chang, et al, Biochem. Biophys. Res. Commun., vol. 99, pp. 745-751 (1981); Jarabak, et al, Prostaglandins, vol. 18, pp. 241-246 (1979), and Lin, et al, Biochem. Biophys. Res. Commun., vol. 81, pp. 1227-1234 (1978), all of which are incorporated herein by reference.

Examples of suitable 15-hydroxyprostaglandin dehydrogenase inhibitors include, but are not limited to, oleic acid, palmitic acid, sulphasalazine and analogues thereof, 15(R)-prostaglandin E-1, 15(R)-prostaglandin E-2, and 15(R)-15-methyl prostaglandin E-2. US Pat. No. 6,103,765, which provides a more extensive discussion of PGDH inhibitors, is hereby incorporated in its entirety.

V. Phosphodiesterase Inhibitors

Suitable phosphodiesterase (PDE) inhibitors for use in the present invention include, but are not limited to, caffeine, aminophylline, theophylline, amrinone, milrinone, vesnarinone, vinpocetine, pemobendan, cilostamide, enoximone, peroximone, rolipram, R020-1724, zaniprast, dipyridamole, MY5445, IC-351 and sildenafil. Type IV phosphodiesterase inhibitors that selectively block the degradation of cGMP are preferred.

VI. Anticholinergic/Antispasmodic Agents

Anticholinergic agents may induce relaxation in the prostatic smooth muscle when applied by the present method. Suitable anticholinergic agents for use in the present invention include, but are not limited to, atropine, scopolamine, glycopyrrolate, hyoscamine, tolterodine and oxybutynin. Agents that relax smooth muscle such as flavoxate, dicyclomine and calcium channel blockers like verapamil are also of benefit in this method.

VII. Anti-Androgens

Suitable anti-androgens for use in the present invention include, but are not limited to, therapeutic compounds such as finasteride, myristoleic acid, palmitoleic acid, oleic acid, myristic acid, lauric acid, linoleic acid, alpha-linolenic acid, gamma-linolenic acid and extracts of Serenoa repens that block the conversion of testosterone to dihydrotestosterone. Blocking the production of this potent androgen is of particular value in both the treatment and prevention of BPH. Gonadotropin-releasing hormone (GnRH), leuprolide and gonadorelin block the production of testosterone and may be of particular value in treating CaP.

The isolated stereoisomers of any of the above agents may demonstrate improved selectivity of therapeutic action and are included in the scope of this invention.

Any single therapeutic compound or a combination of the above-listed compounds, including combinations of different therapeutic groups, may also be used in the present invention, as long as the therapeutic compounds are physically compatible. Particularly desirable combinations of therapeutic compounds are PGEs and alpha-blockers, PGEs and PGDH inhibitors, and PGEs and interferons.

In some instances, it may be advantageous to pre-treat the mammal with one or more of the therapeutic compounds followed by treatment with one or more of the therapeutic compound. For example, pre-treatment with a PGDH inhibitor followed by treatment with PGE will enhance the efficacy of the present method. Additionally, for example, in the treatment of BPH, the prostatic urethra may be treated with infusion of the prostaglandin solution for 10 – 30 minutes followed by infusion of the interferon solution.

Compositions containing an interferon, a 5-alpha reductase inhibitor, chemotherapeutic agents such as tocopherol succinate and vitamin C analogs, muscarinic agents and verapamil are believed to be novel.

The therapeutic compounds can be administered in any conventional form, such as a liquid, solid or gel. Examples of suitable liquids include sterile solutions, suspensions, and emulsions, including creams, ointments, and liposomes. Methods for preparing various dosage

forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed. (Easton, Pa.: Mack Publishing Company, 1990).

In the case of a solid preparation, the carrier may be any solid substance that is compatible with the drug to be administered, releases the drug upon contact with the mucosa and is not irritating to the mucosa as used. Examples of suitable solids include polyethylene glycol (PEG), polyethylene oxide and other low melting point or water-soluble polymers including fatty acid esters made into suppositories or pellets. Preferred PEG suppositories contain a PEG which is solid at ambient or room temperature but rapidly dissolves/melts when placed on the urethra. Long chained fatty acid triglycerides with or without fatty acid esters are well suited to use with this invention.

Examples of suitable gels include triacetin, hydroxycellulose, gels composed of water, propylene glycol, hydroxypropyl methylcellulose and any other gels which are compatible with the therapeutic agent(s). Liposomal mixtures are particularly preferred when one component is lipid soluble and one component is water soluble. The liposomes may be prepared as either anionic or cationic liposomes depending upon the therapeutic compound to be used. A preferred gel for use with prostaglandins is lecithin organogel prepared according to H. Willimann et al, "Lecithin organogel as matrix for transdermal transport of drugs," J. Pharm. Sci., vol. 81(9), pp. 871-874 (1992). Examples of lipophilic liquids that are particularly preferred are triacetin, tricaprin, tricaproin, tricaprylin and mixtures of various triglycerides.

One may also use a gel in which one or more of the therapeutic compounds is released in a controlled-released manner (i.e., released over time) to prolong the effect of the composition. For example, PGE can be formulated into a cross-linked polyethylene oxide/urethane polymer which is well tolerated by living tissues and releases the prostaglandin in a controlled release manner. Controlled release compositions are disclosed in D. H. Lewis, Controlled Release of Pesticides and Pharmaceuticals, Plenum Press, New York, 1981; and A. F. Kydonieus, Controlled Release Technologies: Methods, Theory, and Applications, CRC Press, Boca Raton, 1980, which are incorporated herein by reference.

Cyclodextrin complexes of some therapeutic compounds that are lipid soluble may also be used in order to increase the efficacy. For example, cyclodextrin complexes may be prepared by adding the proper stoichiometric ratio of the prostaglandin or other agent to the cyclodextrin in an aqueous solvent and then either using as is or lyophilizing to provide a solid clathrate for mixing. These complexes are described in Yamamura et al, J. Chromatogr., vol. 331, pp. 383-388 (1985); Hirayama et al, Chem. Pharm. Bull., vol. 32 pp. 4237-4240 (1984); Uekama et al, J.

Pharm. Sci., vol. 73, pp. 382-384 (1984); and Yamamura et al, J. Chromatogr., vol. 303, pp. 165-172 (1984), which are incorporated herein by reference.

Matrix component(s) that are suitable for use in combination with the therapeutic compound(s) may be composed of any material or mixture of materials that is compatible with the therapeutic compound(s) and that releases the therapeutic compound(s) upon insertion into the meatus or urethra. Specific examples of suitable materials for use as matrix components include but are not limited to fatty acid esters, such as ethyl stearate, methyl stearate, isopropyl stearate, butyl stearate, and cetyl lactate; fatty acid ethers, such as laureth 9; cholesterol esters, such as cholesteryl oleate and cholesteryl palmitate; cholesterol ethers; fatty acid diglycerides; fatty acid triglycerides; fatty acids; phospholipids; glycolipids; and sphingolipids. Ethyl stearate and a mixture of methyl palmitate and tripalmitin are particularly preferred compounds for use as matrix components. Another example of a material suitable for use as a matrix component(s) includes materials such as hydrogels which contain or are saturated with the therapeutic agent(s).

The composition comprising the therapeutic compound(s) of the present invention may be applied by any mode of administration allowing for contact between the composition and the mucosal membranes of the lower urinary tract of a mammal, including, but not limited to, application by way of a catheter, a medicated ring, suppository, dropper, syringe, applicator, tube or by spray. When the composition is a liquid, the administration may be accomplished by means of a dropper, syringe or catheter. When the composition is in the form of a gel, lotion, or cream the administration may be carried out by means of a tube, syringe or catheter. Pharmaceutical compositions that contain the therapeutic compound(s) and are in the form of a solid may be administered by inserting the appropriate amount of the solid dose form directly into the urethra or by use of an applicator.

Particularly preferred routes of administration are by application directly to the mucosa of the prostatic urethra and by application to the mucosa of the meatal portion of the penile urethra. As shown in FIG. 1, the male penile urethra consists of three segments: the bulbar urethra, the "trans-urethral" area and the meatal segment. The term prostatic urethral administration as used herein refers to the administration of agents to any portion of the urethra from its origin at the sphincter of the bladder to the membranous urethra. The term meatal administration as used herein refers to the administration of agents to the urethra of the navicular fossa and/or to the penile meatus (as shown in FIG. 1) that are covered by stratified squamous epithelium. Meatal administration is thus essentially the same as topical administration with respect to the difficulty of administering an effective transdermal dose. Meatal administration is considerably easier to carry out than transurethral administration and may be the only possible means of administration

in patients with narrowing or scarring of the urethra. The depth of insertion of the suppository in meatal administration is, as measured from the external opening of the penis, generally between 2 mm and 30 mm depending on individual differences. Insertion of a meatal suppository can be easily and painlessly done by simply pressing the end of the suppository into the meatal opening of the penis. No cumbersome devices are required. Those suppositories containing a matrix material that does not melt or dissolve upon insertion are preferably inserted into the urethra to a depth which leaves a portion of the suppository protruding from the urethra, left in the urethra until the desired effect is achieved, and then removed from the urethra by means of the protruding portion.

The therapeutic compounds of the present invention may also be administered to the mucosal membranes of the prostatic urethra by insertion of a small gauge pediatric catheter through the meatus of the glans penis until the proximal portion of the penile urethra or the distal portion of the intramembranous urethra is reached. Gentle inflation of the distal bulb of the catheter affects occlusion of the urethra and affords a direct route via the central channel of the catheter to the prostatic urethra. Infusion of the prostatic urethra with the therapeutic compound (in the form of a solution) is readily performed by retrograde injection of the solution through the tip of the catheter. Contact is maintained with the prostatic urethra by clamping the catheter to prevent the therapeutic solution from refluxing through the bore of the catheter and by the inflated catheter bulb preventing the drug solution from draining down the urethra. The sphincter of the bladder prevents spillage of the drugs into the bladder (FIG. 4). Volumes of 0.5 – 1.5 mls of solution are well tolerated without leakage of the drug around the inflated bulb of the catheter. Provision for monitoring the pressure in the area of the urethra being treated is made by placing the sensing tip of a pressure transducer into that area through the catheter. This route is quite distinct from the "trans-urethral route" reported by Place in U.S. Pat. Nos. 5,773,020 and 5,919,474 and does not result in undesired side effects such as penile erection. Patients generally report no discomfort and rest or read quietly during the time period over which the catheter is in place. Contact time has varied between 30 –180 minutes. The catheter bulb is deflated at the end of the treatment period and the catheter removed. This method is very well tolerated in an outpatient setting and no adverse effects have been seen to date. A number of 3 way catheters are commercially available and may be utilized within the scope of this invention.

In a third emodiment, the present invention also provides novel devices for the administration of therapeutic compound(s) to the mucosal membranes of the lower urinary tract. Such devices are constructed of a drug reservoir means that in its simplest form is a ring of material containing the therapeutic compound that is placed in the prostatic urethra. This

medicated ring (see FIG. 5) consists of an outer ring of material in direct contact with the prostatic urethral mucosa. This direct contact facilitates drug delivery to the prostate. A central tubular means allows uninterrupted flow of urine from the bladder to the penile urethra. The ring may be made out of any material that allows release of the drug components, including, but not limited to, hydrogels, high melting triglycerides, polyethylene glycols and polyethylene oxides. Materials that allow timed-release of the therapeutic compound such as a hydrogel are preferred. The ring may be made of a bioerodable material that releases the therapeutic compound as the matrix is eroded or other release mechanisms such as an osmotic pillow that swells upon insertion as it absorbs water from the urethra causing release of a solution of the therapeutic compound(s) through controlled diameter apertures or openings in the outside of the ring. Precautions necessary to prevent the hydrogel from swelling and causing obstruction to the flow of urine include limiting the thickness of the hydrogel ring that is placed in the urethra. Alternatively, a ring composed of methyl palmitate and tripalmitin allows timed-release of the therapeutic compounds without swelling. Provisions may be made for retrieval of the ring should it be necessary due to side-effects in a patient or to terminate the effects (by a means to remove such as a string). Alternatively, the ring may be made to adhere to the outer surface of a urinary catheter in the region that will be in contact with the prostatic urethra. Such a catheter may be inserted into the bladder and left in place to continuously release the therapeutic compounds into the prostatic urethra for as long as several days. Another variation of this invention is a double lumen catheter device. One lumen would be continuous with the urinary bladder in order to drain urine as it forms. The second lumen would be connected to a pump and drug reservoir on one end and to a fenestrated or multi-channeled opening on the outside of the catheter in contact with the prostatic urethra. This arrangement allows great latitude in controlling dosing and exposure of the prostate to the therapeutic compounds. This arrangement would be of greatest value in the treatment of CaP and severe cases of BPH.

The compositions of the invention may also be administered directly into the glandular ducts of the prostate via cannulation with an endoscopically placed catheter. Gentle infusion of an aqueous solution of therapeutic compound(s) or placement of a suspension of micro particles containing the therapeutic agent(s) would afford either immediate or sustained release of the drugs into the ductal system. All of the above routes are believed to be novel.

The glans penis is derived embryologically from the same tissue as the meatal urethra and is normally covered by the foreskin. Thus, the glans penis may be considered an extension of the distal urethra for the purpose of this invention. Meatal application of the composition for the purposes of this invention may also be achieved by casting the therapeutic agents into a

suppository and dispensing the suppository to a patient for use at home. Inserting a suppository trans-meatally is effective in delivering the therapeutic compounds to the prostate. This surprising and totally unexpected result affords a novel route of administering therapeutic compounds to the prostate via a minimally invasive procedure.

The preferred method of administration will depend upon whether the goal of treatment is to prevent or to treat a prostate disorder and upon the severity of the prostate disorder. Preferably, for the prevention of prostate disorders the therapeutic compound(s) is administered by the trans-meatal route, for example with a suppository. Suitable candidates for preventative treatment will be patients who have a strong family history of prostate disorders, patients with early evidence of a progressive decline in the maximum urinary flow rate, patients with early symptoms of BPH and any man over the age of 40 in which the treatment is well tolerated. Meatal suppositories may be dispensed for home use making this route ideal for the administration of therapeutic compounds with minimal expense and intrusion into the patient's life.

In one preferred embodiment, the suppository has a round or pointed tip to facilitate entry into the urethra. Alternatively, the suppository may be tapered along all of or at least a substantial part of its length. The base of the suppository may be distended or flared to provide a built-in stop, so that the depth of the insertion may be determined by the length from the tip of the suppository to the beginning of the flare. Alternatively, the base of the suppository may be attached to a piece of foil, plastic or paper or attached to the inside of the tip of a condom in order to set the depth of insertion.

Suppositories for use in connection with the present invention will typically have a cross-section having a maximum dimension of from about 1 mm to about 25 mm, preferably from about 2 mm to about 10 mm, most preferably from about 2 mm to about 6 mm, along the portion of the suppository intended to be inserted into the urethra. Although there is in principal no lower limit on the minimum cross-sectional dimension along the portion of the suppository intended to be inserted into the urethra, practically speaking, the suppository should be thick enough to retain sufficient structural integrity to permit insertion of the suppository into the urethra without breaking or significantly bending the suppository. As noted above, the present suppository may have a shape in which the base of the suppository is distended or flared. The distended or flared portion of the suppository will typically have a minimum dimension of at least about 5 mm, preferably at least about 10 mm. Although there is in principal no upper limit on the maximum cross-sectional dimension of the distended or flared portion of the suppository, practically speaking, it is not necessary to make the distended or flared portion any larger than

what is required to prevent insertion of the suppository into the urethra beyond the point at which the distended or flared portion begins.

For the treatment of prostate disorders with mild or moderate severity of symptoms, the trans-meatal route is preferable. More severe symptomatology or a desire to see more rapid therapeutic effects would make the route utilizing the prostatic urethra preferable. Administration of therapeutic compounds with a narrow therapeutic index may be most safely administered via the prostatic urethra method under the direct supervision of the physician.

The amount of therapeutic compound(s) to be administered will depend upon the exact size and condition of the patient. The therapeutic compounds of the present invention are to be administered in a therapeutically effective amount, which is understood to mean a nontoxic but sufficient amount of the drug or agent to provide the desired effect. For example, an effective amount means the amount that results in improvement in symptom scores or that results in improvement in peak urinary flow rates or in reduction of the serum PSA level in BPH. A therapeutically effective amount in CaP means, for example, the amount that results in reduction in prostate tumor mass or in reduction in serum levels of PSA.

If the therapeutic compound is a prostaglandin, although the exact amount to be administered will depend on the exact size and condition of the patient, the prostaglandin is suitably administered in an amount of from 1 nanogram to 1,400 micrograms, preferably from 1 microgram to 1,000 micrograms, most preferably from 10 to 500 micrograms. Good results have been obtained with prostaglandin E concentrations in the 100 – 1,000 mcg per ml range. The broad ranges of suitable dosages reflect clinical findings that various coagents and carriers can either increase or decrease the drug activity exhibited by a given mixture and that individuals may exhibit different levels of sensitivity to a therapeutic agent. In practice, one would begin with a small dosage amount of a therapeutic agent to ascertain the minimum dosage amount needed for an adequate clinical response and increase dosage amount if needed.

The duration of treatment and time period of administration of the therapeutic agent will also vary according to the size and condition of the patient, the severity of the illness and the specific composition and method being used. For example, typically, the prostaglandin will be administered for 30 – 90 minutes when a catheter based device is used for treatment in a physician's office; for 2 – 72 hours when a controlled release device is used; and, for several hours when a trans-meatal suppository is used. The administration of the trans-meatal suppository will be terminated by urination. Improvement is surprisingly and unexpectedly rapid with dramatic benefits often seen at the end of one treatment. The number of treatments to be given will depend upon the condition being treated, the severity of the condition and the response

of the individual. Excellent responses have been seen with 1 – 5 treatments applied to either the meatal urethra or the prostatic urethra (see Examples).

If the therapeutic compounds are interferons administered in combination with the prostaglandin, the amount of interferon is suitably administered from 100 – 50,000,000 IU, preferably from 1,000 – 10,000,000 IU, most preferably from 100,000 – 2,000,000 per ml. Although the exact amount of interferon to be administered will depend on the exact size and condition of the patient, good results have been obtained by administration of interferon in the range of 100,000 – 2,000,000 IU per ml. The corresponding prostaglandin dosage amount is as described above.

Typically, a composition comprising prostaglandin and interferon will be administered for 30 – 90 minutes when a catheter based device is used; for 2 – 72 hours when a controlled release device is used; and, for several hours when a trans-meatal suppository is used. The administration of the trans-meatal suppository will often be terminated by urination.

In addition to the therapeutic compound(s) discussed above, the composition administered to the mucosal membrane will typically contain one or more pharmaceutically acceptable carriers (also termed "excipients" or "vehicles") suited to the particular type of formulation, i.e., gel, ointment, suppository, or the like. The vehicles are comprised of materials of naturally occurring or synthetic origin that do not adversely affect the therapeutic compound(s) or other components of the formulation. Suitable carriers for use herein include water, silicone, waxes, petroleum jelly, polyethylene glycol, propylene glycol, liposomes, sugars such as mannitol and lactose, and a variety of other materials, depending, again, on the specific type of formulation used.

It may in some cases be desirable or necessary to include a detergent in the formulation, in an amount effective to increase solubility of the therapeutic compound in the vehicle and bioavailability of the compound following administration. The detergent will typically be a nonionic, anionic, cationic or amphoteric surfactant. In the practice of the invention, the surfactant is selected such that local irritation at the site of administration is avoided. Examples of suitable surfactants include Tergitol.RTM. and Triton.RTM. surfactants (Union Carbide Chemicals and Plastics, Danbury, Conn.), polyoxyethylenesorbitans, e.g., TWEEN.RTM. surfactants (Atlas Chemical Industries, Wilmington, Del.), and pharmaceutically acceptable fatty acid esters such as lauryl sulfate and the like.

The formulations may also optionally include one or more components to enhance permeation of the therapeutic compound(s), i.e., "permeation enhancers." Suitable permeation enhancers include those generally useful in conjunction with topical, transdermal or

transmucosal drug delivery. Examples of suitable permeation enhancers include dimethylsulfoxide ("DMSO"), dimethyl formamide ("DMF"), N,N-dimethylacetamide ("DMA"), decylmethylsulfoxide ("C.sub.10 MSO"), polyethylene glycol monolaurate ("PEGML"), glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone.RTM. from Nelson Research & Development Co., Irvine, Calif.), lower alkanols (e.g., ethanol), SEPA.RTM. (available from Macrochem Co., Lexington, Mass.), and surfactants, including, for example, Tergitol.RTM., Nonoxynol-9.RTM. and TWEEN-80.RTM.

In a forth embodiment, the present invention provides kits to administer therapeutic compounds and novel compositions to the mucosal membranes of the lower urinary tract for the treatment and/or prevention of prostate disorders in mammals. The kits are characterized as containing: (a) a means for containing a therapeutic compound or composition comprising a therapeutic compound and (b) a means for administering the compound or composition to the mucosal membranes of the lower urinary tract of a mammal. When the composition is in the form of a suppository, the means for containing the compound or composition may be foil or plastic wrappers surrounding the suppositories that may be placed into a box or carton or other sealed container. The means for containing the compound or composition may be a bottle, canister or plastic tube when the composition is in the form of a liquid, gel, lotion or cream. Rings or catheters containing the compositions may be placed in individual foil or plastic wrappers and then placed into a box or carton. The means for administering the compound or composition may be a catheter, a medicated ring, suppository, dropper, syringe, applicator, tube or by spray. When the composition is a liquid, the administration may be accomplished by means of a dropper, syringe, catheter or finger tip. When the composition is in the form of a gel, lotion, or cream the administration may be carried out by means of a tube, dropper, syringe, catheter or finger tip. Pharmaceutical compositions that contain the therapeutic compound(s) and are in the form of a solid may be administered by inserting the appropriate amount of the solid dose form directly into the urethra, by the use of an applicator or by the finger tip.

It is to be understood that the means for administering the pharmaceutical composition may be connected to or a part of the means for containing the pharmaceutical composition comprising.

Examples of preferred kits include:

A. A kit which includes a container which can hold 1 to 100 unit doses of the compound or pharmaceutical composition and a dropper which can dispense between 0.1 to 1.0

ml as a unit dose. The container is preferably glass, metal or a plastic known not to adsorb hydrophobic compounds.

B. A kit which includes a container which can hold 1 to 100 unit doses of the compound or pharmaceutical composition with an applicator to administer the pharmaceutical composition internally onto the mucosal surface. The container is preferably glass, metal or a plastic known not to adsorb hydrophobic compounds.

C. A kit which includes a tube which holds 1 to 100 unit doses of a compound or pharmaceutical composition, which is in the form of a cream or gel, and an applicator which can dispense a unit dose of the composition.

D. A kit which includes 1 to 100 unit doses of pellets, film or suppositories along with directions for use.

E. A kit which includes 1 to 100 unit doses of urethral rings or catheter devices for administration of the pharmaceutical composition into the prostatic urethra.

The present kits will also typically include means for packaging the container means and the administering means. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc. The present kits will also usually include written instructions that describe how to administer the therapeutic compound or pharmaceutical composition containing the therapeutic compound to the mucosa. It is to be understood that the written instructions may be on any of the container means, the administering means, or the packaging means, in addition to being present on a separate piece of paper.

Other features of the present invention will become apparent in the course of the following description of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

The present invention will be further illustrated in the following, non-limiting Examples. The Examples are illustrative only and do not limit the claimed invention regarding the materials, conditions, process parameters and the like recited herein.

I. Exemplary Formulations:

A matrix material for meatal suppositories composed of 12 – 40 % by weight of tripalmitin in methyl palmitate makes a versatile carrier for the therapeutic compound(s) in this method. A meatal suppository may be easily formed by combining 20 grams of tripalmitin with 80 grams of methyl palmitate and melting at 80° C. Lipophillic therapeutic compounds may

simply be added to this melted matrix material with stirring and then cast into suppositories by any standard method. Therapeutic compounds that are not lipid soluble may be added in a volatile solvent such as ethanol with stirring and rapidly cast into suppositories. Residual alcohol is removed by application of a vacuum to the solid suppository. Solvents such as 1,2 propanediol may be added to the matrix material to increase the solubility of the therapeutic compound and left as a component of the final product. The co-solvent or volatile solvent to be used may be found by experimenting or by consulting references regarding chemical solubility of a therapeutic compound.

Matrix material with higher proportions of tripalmitin (above 20 %) exhibit delayed drug release properties. By the method above, delayed release devices for either meatal or prostatic urethral administration may be easily cast.

In a preferred embodiment, the matrix component is a material or mixture of materials that results in the final composition having a melting point ranging from about 70° F to about 100° F, preferably from about 70° F to about 90° F.

Example 1

A base matrix was formed by melting 0.760 grams of tripalmitin and 3.240 grams of methyl palmitate at 80 °C with stirring. This 18 % tripalmitin matrix melts and releases any contained therapeutic agent on contact with the warmth of the urethra.

Example 2

To 4.000 grams of the molten matrix from Example 1 was added 4.0 milligrams of PGE-2 with stirring. The solution was drawn into a 2.1 mm diameter rigid tube made of high density polyethylene and allowed to cool to room temperature. One hundred unit doses containing 40 micrograms of PGE2 resulted from cutting the tubing at 12 mm lengths. The outer sleeve of polyethylene was left in place to add strength to the soft meatal suppositories. The suppository is pushed out of one end of the protective sleeve and inserted by hand to use. Any standard method of casting suppositories may also be used. This technique works well with any prostaglandin or other lipid soluble therapeutic compound.

Example 3

To the molten mixture of Example 2 containing tripalmitin, methyl palmitate and PGE-2 was added the dry powder from one vial of 25 million IU Intron A™ with rapid stirring. This suspension is rapidly cast into suppositories as in Example 1. One hundred unit doses containing 40 micrograms of PGE-2 and 250,000 IU interferon alpha –2b are thus made. The PGE-2 is rapidly released from the matrix. The solid particles containing interferon alpha-2b are then released by the melting matrix and will slowly dissolve in the moisture of the urinary tract. This

simple preparation thus enables the release of the PGE-2 dissolved in the matrix first followed by the suspended interferon particles without the use of a catheter and sequential infusions. The same result may be obtained with any lipid insoluble therapeutic agent that is a solid at room temperature. One may also use the pure interferon powder if available or may substitute a dried liposomal preparation of the therapeutic agent in this method with excellent results. This preferred embodiment may be administered at home by the patient or may be cast as a ring around a catheter by allowing the suspension to cool and solidify around that portion of a catheter that will be in contact with the prostatic urethra.

Example 4

To the molten mixture in Example 1 was added 15 milligrams of prazosin hydrochloride dissolved in ethanol with stirring. The solution was rapidly cast and produced one hundred unit doses containing 150 milligrams of prazosin hydrochloride. The residual ethanol was removed from the suppositories after solidification by vacuum. Any therapeutic agent that is not lipid soluble may be cast into suppositories by selection of a suitable volatile solvent.

Example 5

To a molten mixture 1 gram of tripalmitin and 3 grams of methyl palmitate was added 200 milligrams of oleic acid, 200 milligrams of palmitic acid and 100 milligrams of gama-linolenic acid with stirring until all were dissolved. Casting yielded 100 suppositories containing 2.0 milligrams of oleic acid, 2.0 milligrams palmitic acid and 1.0 milligram of gamma-linolenic acid. Similar preparations made be made with one or a combination of fatty acids. This preparation releases PGDH and 5alpha-reductase inhibitors into the urethra.

Example 6

To the molten matrix of Example 1 was added 5.0 milligrams of finasteride with stirring until dissolved and then cast into one hundred suppositories containing 50 micrograms of finasteride each.

Example 7

Verapamil hydrochloride was dissolved in water and sodium hydroxide solution added until pH 10. The liberated free base verapamil was extracted with chloroform, The chloroform extract was dried over molecular sieves and evaporated to give the pale yellow liquid free base Verapamil. To the molten matrix in Example 1 was added 75 milligrams of Verapamil with stirring and cast to yield one hundred suppositories containing 750 micrograms of Verapamil each. This free base form of Verapamil is absorbed much more rapidly than the available hydrochloride salt from the mucosa of the lower urinary tract. Many therapeutic agents are made into such salts for oral administration. The present invention is best used with either the free

base or the free acid form of such agents since the un-ionized form is absorbed more rapidly from a mucosal surface. The alpha blockers and many anti-cholinergic agents listed above may be incorporated by this method.

Example 8

Five milligrams of either tolterodine, oxybutynin, or doxazosin prepared in a free base form as generally described in Example 7 are added in the minimal amount of ethanol to the molten matrix of Example 1 with stirring and cast into one hundred suppositories. The ethanol is removed by vacuum to give unit doses of 50 micrograms of the therapeutic agent.

Example 9

To 4 grams of the molten matrix from Example 1 was added 10 milligrams of free base sildenafil in chloroform with stirring and the mixture was rapidly cast. Removal of solvent gave one hundred suppositories containing 100 microgram doses of sildenafil.

Example 10

To 4 grams of the molten matrix from Example 1 was added 20 milligrams of ascorbyl palmitate and 100 milligrams of alpha-tocopherol succinate in ethanol with stirring and the mixture cast and placed in vacuo to give one hundred suppositories containing 0.2 and 1.0 milligrams respectively of the therapeutic agents.

Example 11

The formulations of Examples 2 -10 may be made by substituting triacetin for the solid matrix material. The resultant liquid preparations may be instilled into the prostatic urethra or applied topically to the glans penis.

Example 12

The formulations of Examples 2-10 may be made by substituting a matrix of 30 % tripalmitin and 70 % methyl palmitate in order to afford preparations with delayed release properties.

Example 13

The formulations of Examples 2-10 may be made as liposomal preparations as a substitute for the solid matrix. These rapidly bioavailable preparations may be used on any mucosal surface of the urinary tract but will be particularly potent when infused into the prostatic urethra.

II. Subjective Examples

Example 14

A 56-year-old male with a history of BPH, diabetes mellitus and male erectile dysfunction (MED) presented with marked penile deviation from penile nodules (Peyronie's disease) and symptoms of urinary tract obstruction from BPH including hesitancy, decreased urinary force and dribbling. He had a series of nine treatments that entailed insertion of a soft #12 pediatric Foley catheter 8cm. into the penis, occlusion of outflow from the urethra by constriction with a loose latex band, infusion of a saline solution of PGE2 at pH 6.5 (500 mcg/ml concentration) – total dose 100 mcg PGE2 followed 15 minutes later by 250,000 IU of Intron A (interferon alpha 2b) and allowing 30 minutes for absorption of the treatment. Care was taken to use the minimal amount of compression necessary to prevent leakage of the drug from the urethra so as to not cause is ischemia of the penis.

No adverse effects were seen. The patient experienced immediate and unexpected improvement in his urinary symptoms and marked improvement in erectile function with lessening of the degree of penile curvature over the next 2 weeks, decrease in serum PSA and prolonged beneficial effects months later.

Example 15

A 53-year-old male presented for evaluation of MED. He had had bilateral "penile straightening" surgery 10 years earlier for removal of penile plaques. No plaques were present on exam and the surgical results appeared excellent. Penile ultrasound revealed venous leakage as an etiology of his MED. A 12 French pediatric Foley catheter was placed in the penile urethra and advanced until halted by the massively enlarged prostate gland. The catheter was moved out 5 cm to place the tip roughly before the membranous urethra. Inflation of the catheter bulb with ~ 1.5 ml of saline to occlude the urethra was accomplished without discomfort (see FIG. 4). The lumen of the catheter was clamped to prevent drainage of the therapeutic agents and infusion of the prostatic urethra with 0.5 ml of normal saline at pH 4.9 containing was accomplished by injecting the solution into the lumen of the catheter proximal to the clamp. The PGE-2 solution was thus delivered through the catheter tip and allowed to remain in place for 30 minutes before infusion of 0.5 ml (5 million IU) of Intron A™. After 30 minutes, the dead volume of the catheter was flushed with 0.5 ml normal saline and treatment continued for 30 minutes before deflating the catheter bulb and removing it. No adverse effects were seen. The patient experienced immediate improvement in his BPH symptoms and improvement from an average urinary flow rat before the 1st treatment of 3.5 ml/sec to 30 ml/sec after. He empirically received 2 more treatments at weekly intervals. PSA prior to treatment was 4.0 and after was 2.1

indicating a dramatic reduction in prostate tissue following the therapy. It appears that this result was equivalent to a chemical prostatectomy. His symptoms of BPH and ED cleared totally and he remains asymptomatic almost two years later.

Example 16

A 90-year-old male with severe BPH and a number of other medical problems that made him a poor surgical candidate had a pre-treatment PSA of 10.5, prostate biopsies demonstrating only BPH and had urodynamics demonstrating severe obstruction with the peak urinary flow rate of 5 ml/sec and average urinary flow rate of 2 ml/sec prior to treatment (see FIG. 3 C). Three treatments as outlined in Example 15 were given without complication. Repeat urodynamics after the 3rd treatment showed a peak flow of 8 ml/sec (60 % improvement) and an average flow of 4 ml/sec (100 % improvement). PSA levels dropped by 32 % to 6.8 with some improvement in clinical symptomatology seen. This patient's results are also consistent with a marked reduction in prostate tissue mass induced by the present method and leading to clinical improvement in obstructive symptoms.

Example 17

A 51-year-old male with poorly controlled insulin dependent diabetes mellius, erectile dysfunction, BPH and normal PSA levels (0.3) was given three treatments as outlined in Example 15. FIG. 3 B illustrates his urodynamics study just prior to the 1st treatment and FIG. 3 A illustrates his repeat study after a single treatment. Peak urinary flow rates more than doubled from 12 ml/sec to 25 ml/sec! Thus, a single 90 minute treatment gave better results than reported with TURP (results in Example 15 were even better). PSA was low at the beginning and remained the same later. The patient resolved all symptomatology of BPH with the three treatments.

Example 18

A 52-year-old male with mild symptoms of BPH was sent home with suppositories made as in Example 3 to insert meatally every 2nd or 3rd night. The patient reported improvement in his symptoms after the 3rd treatment.

Example 19

Men who are at high risk for BPH are given suppositories made as in Example 5 to be inserted in the meatus nightly. It is expected that these men will show a significantly lower rate of development of BPH over the next 5 – 10 years.

Example 20

Men who are at high risk for CaP are given suppositories made as in Example 10 to be inserted into the meatus nightly or every 2nd night. It is expected that these men will show a significantly lower rate of the development of CaP over the next 5 – 10 years.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention specifically described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A method for preventing and treating prostate disorders in a mammal comprising administering to the mucusal membranes of the lower urinary tract of the mammal a therapeutically effective amount of a therapeutic compound.

2. The method of claim 1, wherein the therapeutic compound is one or more compounds selected from the group consisting of autocoids, cytokines, chemotherapeutic agents, alpha-receptor antagonists, prostaglandin dehydrogenase inhibitors, phosphodiesterase inhibitors, anticholinergic and antispasmodic agents, and anti-androgens.

3. The method of claim 1, wherein the therapeutic compound is a prostaglandin and an interferon.

4. The method of claim 3, wherein the prostaglandin is PGE-1, PGE-2, PGE-3, misoprostol, misoprostanoic acid, PGA-1, PGA-2, PGJ2, Δ12-PGJ-2, 15-deoxy-Δ12,14-PGJ-2, PGD-2 or 15-deoxy-Δ12,14-PGD-2.

5. The method of claim 3, wherein the interferon is interferon alpha-2a, interferon alpha-2b or interferon gamma-1b.

6. The method of claim 1, wherein the therapeutic compound is a prostaglandin E compound and an alpha-receptor antagonist.

7. The method of claim 1, wherein the therapeutic compound is a prostaglandin E compound and prostaglandin dehydrogenase inhibitor.

8. The method of claim 2,wherein the therapeutic compound is a chemotherapeutic agent selected from the group consisting of tocopherol, alpha-tocopherolsuccinate, vitamin C and analogs thereof, retinol and vitamin A analogs.

9. The method of claim 1, wherein the therapeutic compound is selected from the group consisting of a 5-alpha reductase inhibitor, anti-muscarinic agent, and verapamil.

10. The method of claim 1, wherein the therapeutic compound is administered directly to the mucosa of the prostatic urethra.

11. The method of claim 10, wherein the therapeutic compound is administered directly to the mucosa of the prostatic urethra by way of a catheter.

12. The method of claim 1, wherein the therapeutic compound is administered to the meatal portion of the penile urethra.

13. The method of claim 1, wherein the therapeutic compound is administered by a drug reservoir means.

14. The method of claim 1, wherein the therapeutic compound is administered by a catheter.

15. The method of claim 1, wherein the therapeutic compound is administered by a suppository.

16. A composition comprising a prostaglandin compound and an interferon.

17. A composition in the form of a suppository comprising tocopherol analogs.

18. A composition in the form of a suppository comprising vitamin C analogs

19. A device for the administration of a therapeutic compound to the mucosal membranes of the lower urinary tract of a mammal comprising a drug reservoir means containing the therapeutic compound for insertion into the prostatic urethra.

20. The device of claim 19, wherein the drug reservoir means comprises a medicated ring comprising:

a. an outer ring of material that is in contact with the prostatic urethral mucosa, and

b. a central tubular means allowing uninterrupted flow of urine from the bladder to the penile urethra.

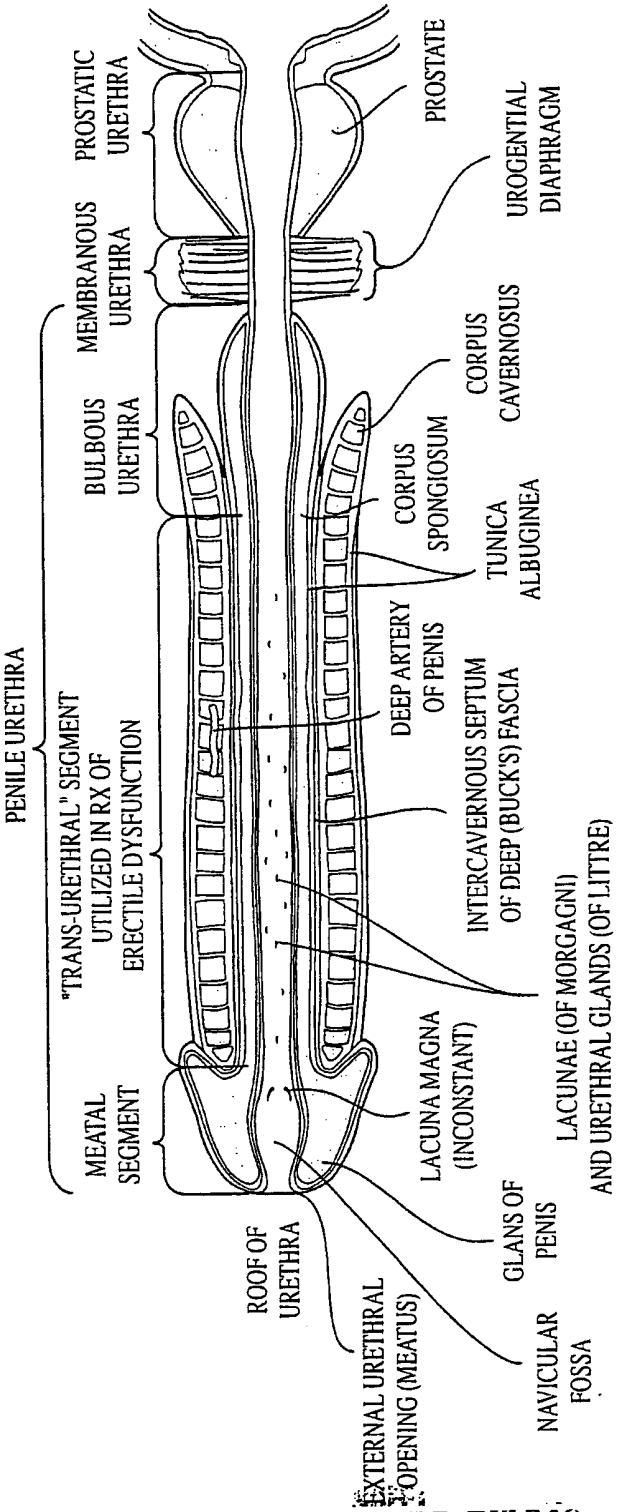

PENILE URETHRA
"TRANS-URETHRAL" SEGMENT UTILIZED IN RX OF ERECTILE DYSFUNCTION
MEATAL SEGMENT
BULBOUS URETHRA
MEMBRANOUS URETHRA
PROSTATIC URETHRA
PROSTATE
UROGENTIAL DIAPHRAGM
CORPUS CAVERNOSUS
CORPUS SPONGIOSUM
TUNICA ALBUGINEA
DEEP ARTERY OF PENIS
INTERCAVERNOUS SEPTUM OF DEEP (BUCK'S) FASCIA
LACUNA MAGNA (INCONSTANT)
LACUNAE (OF MORGAGNI) AND URETHRAL GLANDS (OF LITTRE)
GLANS OF PENIS
ROOF OF URETHRA
NAVICULAR FOSSA
EXTERNAL URETHRAL OPENING (MEATUS)

FIG. 1A

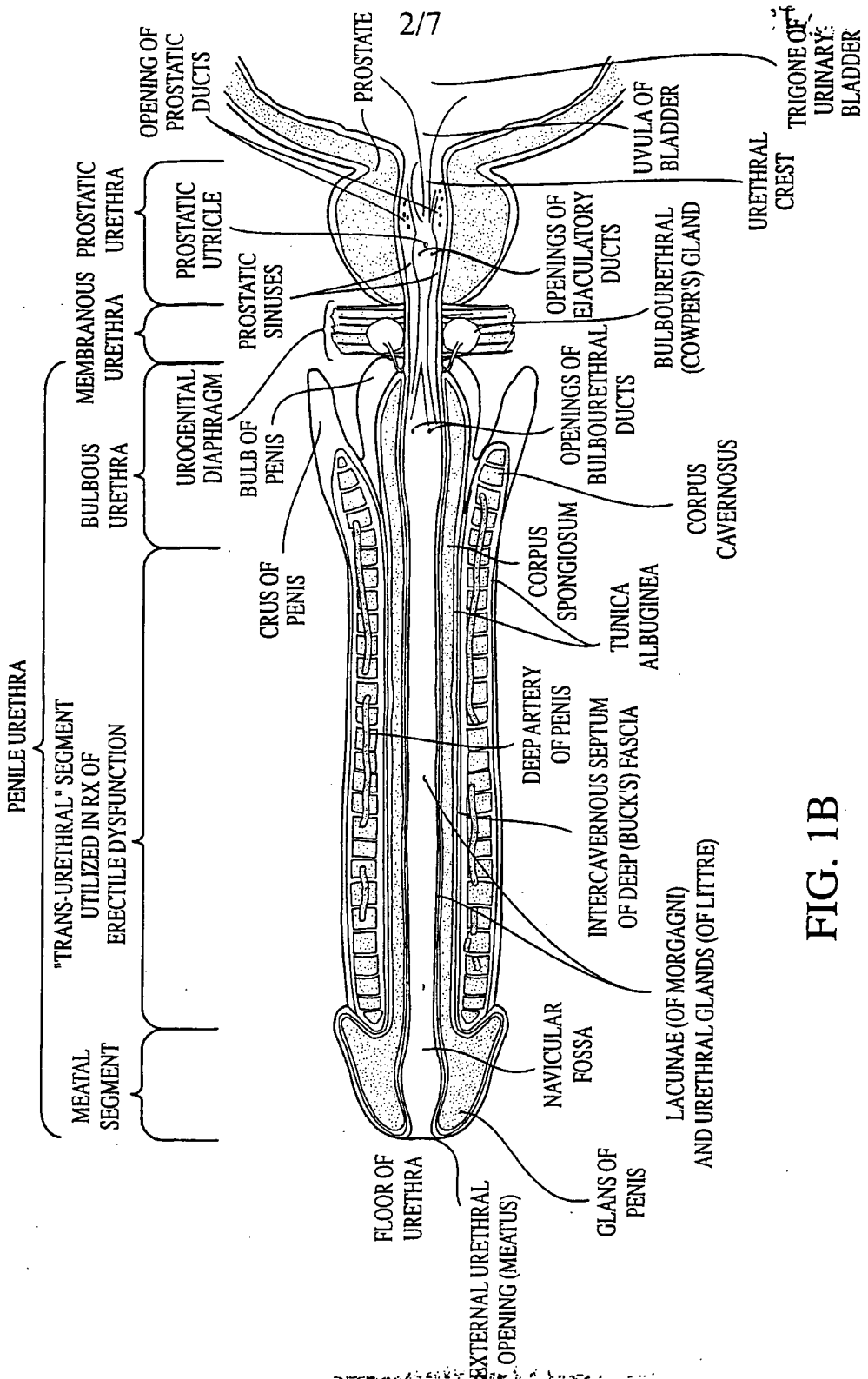

PENILE URETHRA
"TRANS-URETHRAL" SEGMENT UTILIZED IN RX OF ERECTILE DYSFUNCTION
MEATAL SEGMENT
BULBOUS URETHRA
MEMBRANOUS URETHRA
PROSTATIC URETHRA
OPENING OF PROSTATIC DUCTS
PROSTATIC UTRICLE
PROSTATIC SINUSES
UROGENITAL DIAPHRAGM
BULB OF PENIS
CRUS OF PENIS
PROSTATE
OPENINGS OF EJACULATORY DUCTS
OPENINGS OF BULBOURETHRAL DUCTS
BULBOURETHRAL (COWPER'S) GLAND
UVULA OF BLADDER
URETHRAL CREST
TRIGONE OF URINARY BLADDER
CORPUS SPONGIOSUM
CORPUS CAVERNOSUS
TUNICA ALBUGINEA
DEEP ARTERY OF PENIS
INTERCAVERNOUS SEPTUM OF DEEP (BUCK'S) FASCIA
NAVICULAR FOSSA
LACUNAE (OF MORGAGNI) AND URETHRAL GLANDS (OF LITTRE)
FLOOR OF URETHRA
GLANS OF PENIS
EXTERNAL URETHRAL OPENING (MEATUS)

FIG. 1B

FIG. 2

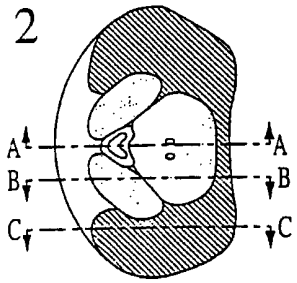


FIG. 2A

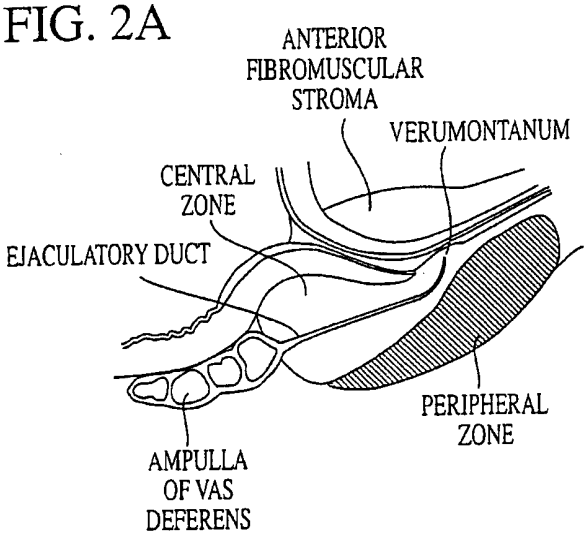


FIG. 2B

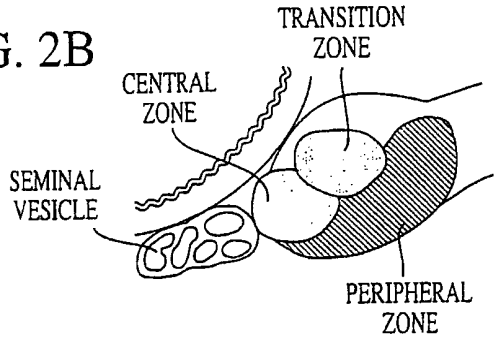
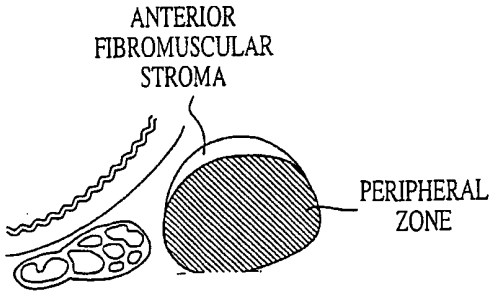


FIG. 2C



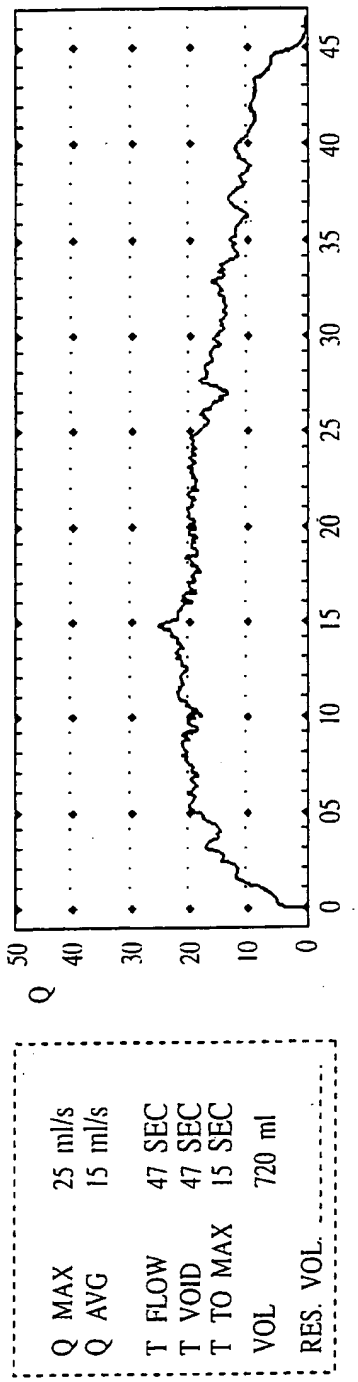

NORMAL PEAK FLOW
Q
50
40
30
20
10
0
0
05
10
15
20
25
30
35
40
45
SEC
Q MAX 25 ml/s
Q AVG 15 ml/s
T FLOW 47 SEC
T VOID 47 SEC
T TO MAX 15 SEC
VOL 720 ml
RES. VOL.

FIG. 3A

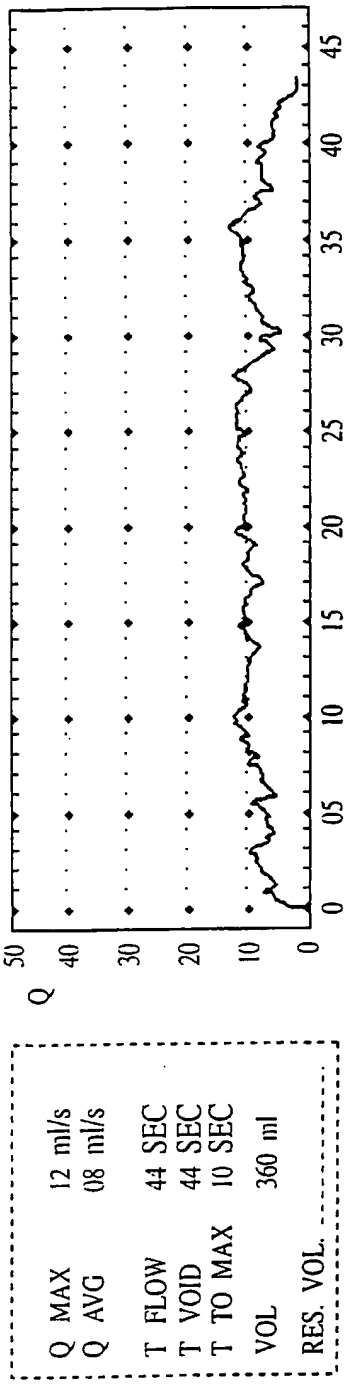

MODERATELY IMPAIRED PEAK FLOW
Q
50
40
30
20
10
0
0
05
10
15
20
25
30
35
40
45
SEC
Q MAX 12 ml/s
Q AVG 08 ml/s
T FLOW 44 SEC
T VOID 44 SEC
T TO MAX 10 SEC
VOL 360 ml
RES. VOL.

FIG. 3B

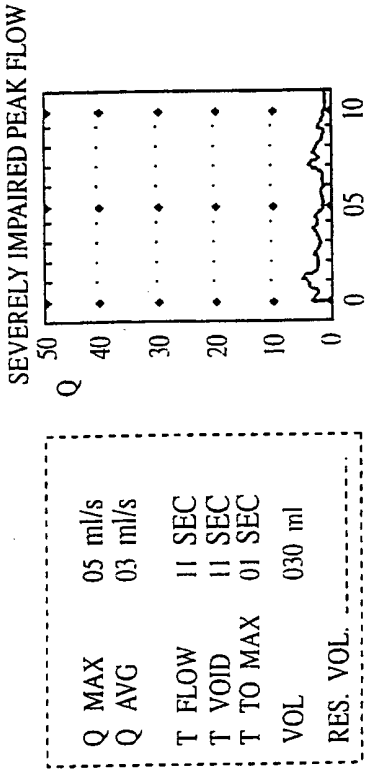

SEVERELY IMPAIRED PEAK FLOW
Q
50
40
30
20
10
0
0
05
10
SEC
Q MAX 05 ml/s
Q AVG 03 ml/s
T FLOW 11 SEC
T VOID 11 SEC
T TO MAX 01 SEC
VOL 030 ml
RES. VOL.

FIG. 3C

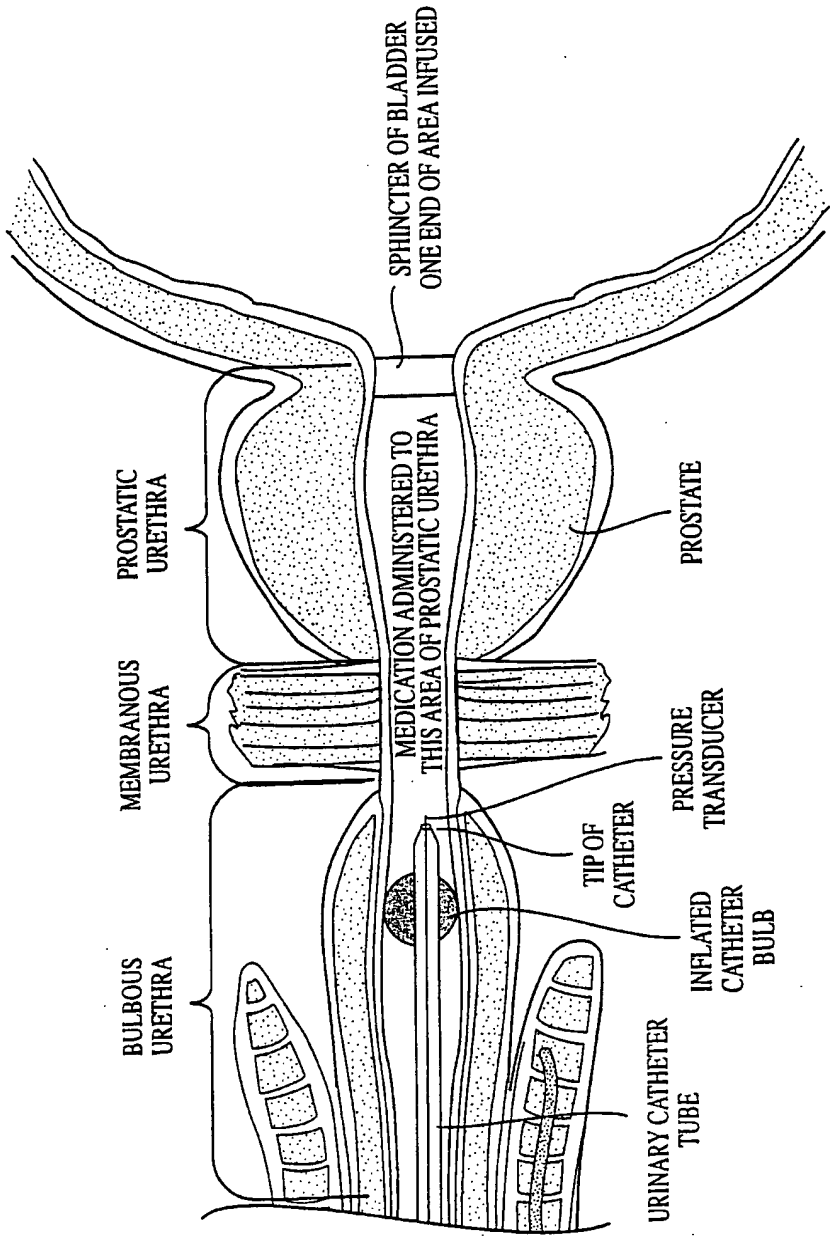

SPHINCTER OF BLADDER
ONE END OF AREA INFUSED
PROSTATIC URETHRA
MEMBRANOUS URETHRA
BULBOUS URETHRA
MEDICATION ADMINISTERED TO THIS AREA OF PROSTATIC URETHRA
PROSTATE
PRESSURE TRANSDUCER
TIP OF CATHETER
INFLATED CATHETER BULB
URINARY CATHETER TUBE

FIG. 4

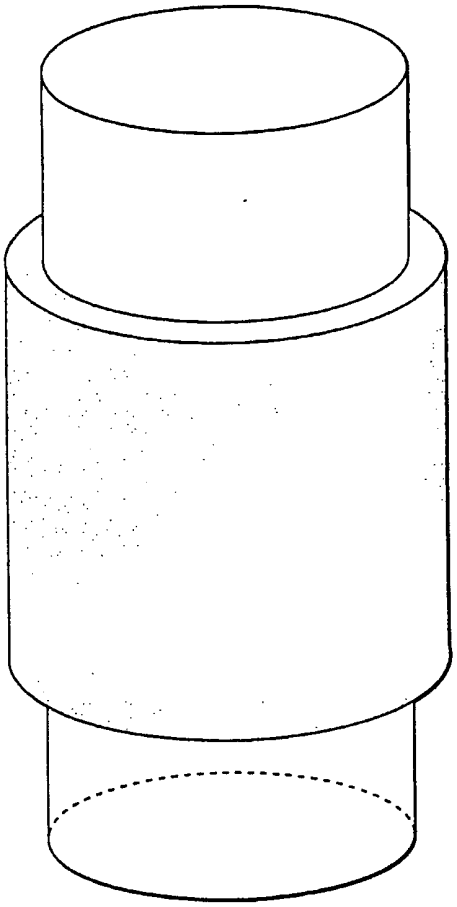


FIG. 5